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Type 2 asthma paediatric patients eligible for dupilumab: An Italian biomarker-based analysis

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ABSTRACT

Background: Type 2 inflammation is the principal determinant of asthma in children, and it leads to the downstream activation of eosinophils (EOS), the production of immunoglobulin-E (IgE), and increased levels of fraction of exhaled nitric oxide (FeNO). Dupilumab received the approval for the treatment of uncontrolled severe Type 2 asthma in children.

Objective: The aim of this analysis was to calculate the Type 2 severe asthma paediatric population who would be eligible for treatment with dupilumab in Italy and characterize them by expected biomarker status.

Methods: The calculation of the dupilumab-eligible population employed a two-phase approach: 1) estimating the total number of children aged 6–11 years with uncontrolled severe asthma; and 2) stratifying the severe uncontrolled asthma population, based on appropriate biomarker levels, thus identifying patients eligible for treatment with dupilumab. The VOYAGE study provided the data for this analysis.

Results: The two-phase approach utilizing VOYAGE data revealed that the average number of paediatric patients with uncontrolled severe asthma was N = 1007. Stratification of these patients, as per VOYAGE data, indicated that the majority (N = 740; 73.5%) would have ≥2 elevated biomarkers, and over one-third patients (N = 434, 43.1%) would exhibit simultaneously elevated levels of EOS, FeNO and IgE. Of the paediatric patients, N = 864 were identified as eligible to dupilumab treatment, constituting 85.8% of the target population. Notably, nearly half eligible patients (N = 454) displayed elevated levels of both EOS and FeNO biomarkers, while the substantial majority (81.1%) exhibited at least an increase of EOS levels (N = 817). Patients with increased FeNO levels without a concurrent increase in EOS were less frequent (N = 47; 5.4% of the eligible population).

Conclusion: The simultaneous testing of multiple biomarkers during baseline patient assessment and disease follow-up is highly recommended. Utilizing cost-effective tests, physicians can estimate the prevalence of severe Type 2 asthma, categorize patients into distinct phenotypes (eosinophilic, allergic, or mixed), and consequently identify and prescribe the most suitable

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therapeutic interventions. This approach also facilitates the ongoing evaluation and adjustment of the treatment strategies based on individual patient responses.

Keywords: Type 2 asthma, Dupilumab, Biomarker, Italy

INTRODUCTION

Asthma presently impacts 8.6% of children under the age of 18 years in the United States.[1] In Italy, findings from the SIDRIA (Studi Italiani sui Disturbi Respiratori dell'Infanzia e l'Ambiente) Study, the largest Italian epidemiological survey of children, conducted between 1994 and 2002, based on questionnaire responses, indicated a prevalence of approximately 9% for lifetime asthma in children aged 6–7 years. These results suggest a tendency towards a stabilization of asthma prevalence in this age group.[2,3]

Around 5–10% of children diagnosed with asthma exhibit characteristics indicative of severe disease.[4,5] Severe asthma in children is marked by a high degree of heterogeneity, encompassing multiple clinical phenotypes and contributing to substantial morbidity.[5] The heterogeneity observed in asthma concerning its onset, natural progression, and response to treatment, poses a notable challenge in devising effective strategies to mitigate the global burden of asthma. Given that, there is a growing interest in identifying potential biomarkers or other indicators to enable more personalized therapeutic approach. Notably, some patients may exhibit a simultaneous presence of multiple biomarkers. In children, type 2 inflammation serves as a predominant driver of asthma and it is characterized by the release of signature cytokines, namely interleukin-4, interleukin-5, and interleukin-13. This cascade of events which results in the activation of eosinophils (EOS), the production of immunoglobulin-E (IgE), and elevated levels of fraction of exhaled nitric oxide (FeNO). The Global Initiative for Asthma (GINA) recommends the utilization of an elevated peripheral-blood eosinophil count ($\geq$150 cells per cubic millimeter), an elevated FeNO ($\geq$20 parts per billion [ppb]), or a combination of both criteria, to identify individuals with severe, uncontrolled asthma who may benefit from biologic therapies targeting type 2 inflammation (NCT02948959).[6]

In line with evidence-based guidelines, the recommended treatment approach for children with severe asthma involves the use of higher-dose inhaled corticosteroids (ICS) or oral corticosteroids in conjunction with a second controller, such as long acting beta-agonists (LABAs), leukotriene antagonists, and theophylline.[7]

However, management of severe patients is linked to unpredictable clinical outcomes, high risk of complications and long-term contraindications.[4,7,8] As a consequence, approximately half of these patients experienced inadequate control of the disease.[9] In response to this unmet medical need and with the aim of enhancing the prognosis of patients with uncontrolled severe asthma, several biologic therapies have been developed.[10]

Dupilumab, a monoclonal antibody targeting the Interleukin (IL)-4 receptor α-subunit, functions as an antagonist against both IL-4 and IL-13.[11] This biologic treatment has proven to be effective and safe in the management of severe asthma. Presently, its use is approved in adults, adolescents, and children with severe asthma with type 2 inflammation (characterised by raised blood EOS and/or increased FeNO), who exhibit inadequate control despite being on medium to high dose ICS in combination with another maintenance medicinal product.[11]

Dupilumab is the first biologic treatment with a broader indication than other biologics. In fact, it is authorized for the treatment of patients with type 2 inflammation asthma, including different phenotypes. The Liberty Asthma VOYAGE, a phase 3 multinational, controlled with placebo, randomized trial (Evaluation of Dupilumab in Children with Uncontrolled Asthma, ClinicalTrials.gov: NCT02948959), was designed to evaluate dupilumab's effectiveness and safety in children aged 6–

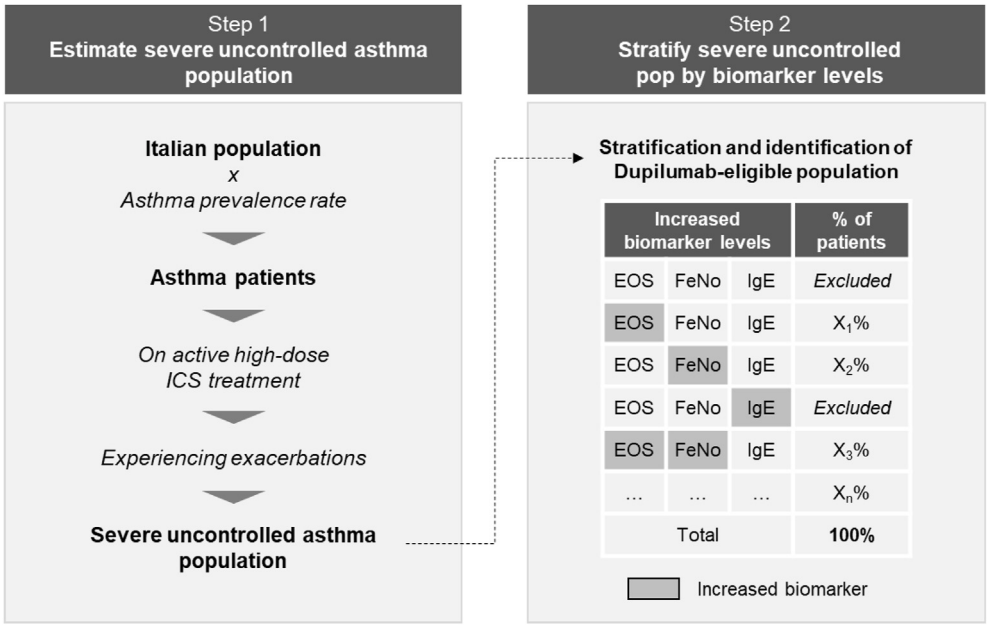

Fig. 1 Methodological approach to estimate dupilumab-eligible population in Italy (illustrative).

11 years dealing with moderate-to-severe asthma. This study demonstrated that, children with uncontrolled moderate-to-severe asthma, who received add-on dupilumab had fewer asthma exacerbations and better lung function and asthma control than those treated with placebo.

In 2021, a Canonica et al study[12] estimated the dupilumab-eligible population in Italy and characterized it based on the biomarker status. In that study, stratification of patients by biomarkers status was guided by the outcomes of the QUEST study, a phase 3 study, controlled with placebo and with a follow-up of 52 weeks (LIBERTY ASTHMA QUEST ClinicalTrials.gov number, NCT02414854).

In this paper we aimed to replicate the methodological framework employed in the study conducted by Canonica et al, in order to: 1) assess the number of paediatric patients with Type 2 severe asthma in Italy who meet the eligible criteria for dupilumab treatment based on the approved indication, and 2) profile the paediatric population eligible for dupilumab by their anticipated biomarker status. The principal source for this study is the VOYAGE study.

METHODS

The present analysis was conducted using a two-phase approach (Fig. 1): 1) estimation of the paediatric patients aged 6–11 years experiencing uncontrolled severe asthma; and 2) classification of the population with severe uncontrolled asthma by relevant biomarker levels and identification of dupilumab-eligible patients.

Data sources

Phase 1

The estimation of the number of children affected by asthma in Italy was carried out applying a prevalence rate of 6.1% to the Italian population aged 6–11 years.[13] This prevalence rate was derived from the 2019 Italian-adapted GINA (Global Initiative for Asthma) guidelines and originally pertains to patients above 15 years old.[7] In the absence of recent Italian epidemiological data specifically for children, this rate was deemed appropriate for the analysed paediatric population as well.

The analysis carried out by Region Veneto in 2016[14] was the primary reference used to determine the proportion of patients with severe uncontrolled asthma from the overall asthmatic paediatric population.

The regional analysis considered the following inclusion criteria to select the severe uncontrolled asthma patients: 1) having an asthma exemption code; 2) undergoing spirometry; 3) receiving active pharmacological treatment with ICS + LABA, and/

or theophylline and/or leukotriene receptor antagonists; 4) undergoing high-dose ICS treatment (prescription of ICS maximum dose); 5) demonstrating high-rate adherence (annual coverage level ≥80%); and 6) experiencing disease exacerbations (≥2 episodes/year of inpatient admission or receiving systemic corticosteroids therapy for >3 days in the ambulatory setting). The relevant codes for patients inclusion are reported in Supplemental Table 1 in the Supplemental Materials. In the context of the Region Veneto analysis, the comprehensive prevalence of severe refractory asthma is equal to 0.034%. The patient-funnel approach outlined in the present analysis is detailed in Table 1.

Phase 2

In the second phase of the analysis, the paediatric population with severe uncontrolled asthma was categorized based on biomarker levels. This phase is essential to pinpoint patients that present blood EOS<150 cells/μL and FeNO<20 ppb levels. As a matter of fact, according to dupilumab indication, these patients must be excluded from eligible population estimation. The primary source considered to evaluate the distribution of paediatric patients based on Type 2 inflammation biomarkers (EOS, FeNO, and IgE) was the VOYAGE trial, a double-blind, randomized, placebo-controlled trial evaluating the efficacy of dupilumab in paediatric patients with uncontrolled moderate-to-severe asthma (NCT02948959).[6]

RESULTS

Based on the data gathered through the 2-phase approach, about 193 thousand paediatric patients (6–11 years old) with asthma live in Italy (Table 1; line 2). Adopting Region Veneto approach to the Italian paediatric population, it is estimated that ∼70 thousand patients have an exemption code for asthma. Among them, ∼19 thousand undergo at least 1 spirometry per year (27.7%), and almost half of this group (9 thousand) receive ICS treatment. Around 0.03% of these patients[15] are identified with uncontrolled asthma, corresponding to N = 948–1066 patients (Table 1, lines 8 and 9, respectively).

The present analysis estimates an average number of paediatric patients affected by uncontrolled severe asthma equal to N = 1007. This corresponds to 5% of all paediatric patients with asthma who perform regular follow-up (ie, patients with spirometry) and 11% of actively treated

#	Group of subjects	Estimation	Number of subjects (N)	Source
1	Italian paediatric population, 6–11 years	–	3,148,955	ISTAT 2022[13]
2	Patients with asthma	6.10% of #1	192,873	14
3	Patients with asthma exemption code	36.29% of #2	69,880	
4	Patients with spirometry (last 12 months)	27.74% of #3	19,386	
5	Patients treated with ICS+2nd controller	46.95% of #4	9100	
6	Patients treated with high-dose ICS+2nd controller	43.05% of #5	3917	
7	Patients treated with high-dose ICS, adherent	57.20% of #6	2241	
8	**Uncontrolled patients with ≥2 exacerbations/year**[a]	47.57% of #7	**1066**	
9	**Uncontrolled patients with severe asthma**	0.03% of #1	**948**	14
10	**Average number uncontrolled patients with severe asthma**	Average of #8 and #9	**1007**	Calculated

Table 1. Estimation of patients with severe uncontrolled asthma in Italy [Sources: see table]. *ICS: Inhaled Corticosteroids; ISTAT: Italian Institute of Statistics.* [a]*Corresponding to 0.034% of the Italian population, 6–11 years (#1).*

paediatric asthmatic patients (ie, patients receiving ICS).

In the second phase of the analysis, the stratification of patients by biomarker levels was assessed. Fig. 2 presents a visual illustration of the distribution of paediatric patients based on biomarker status, as per the data from the VOYAGE trial.

In the VOYAGE trial, it was observed that 81.1% of the total paediatric patients had EOS≥150 cells/µL; 49.8% had FeNO≥20 ppb and 71.6% exhibited allergic status (IgE≥100 IU/mL). Generally, two major groups emerged: i) patients with an increase in both EOS and FeNO levels (EOS≥150 cells/µL and FeNO≥20 ppb), combined with allergic status (IgE≥100 IU/mL), representing the 43.1% of the patient population; and ii) patients with EOS≥150 cells/µL, FeNO<20 ppb and allergic status (IgE≥100 IU/mL) representing the 26.2% of the patient population. Considering that a specific level of biomarkers were not required as inclusion criteria in the VOYAGE study, the observed distribution may reflect the general population.

Two patient groups were considered not in alignment with dupilumab indication and, therefore, not eligible for the treatment: i) patients with EOS<150 cells/µL, FeNO<20 ppb and allergic status (IgE≥100 IU/mL; 4.2% of paediatric asthmatic patients); and ii) patients with EOS<150 cells/µL, FeNO<20 ppb and non-allergic (IgE<100 IU/mL; 10.0% of paediatric asthmatic patients).

The stratification of the N = 1007 paediatric patients, according to VOYAGE patients characteristic at baseline, is presented in Table 2. A majority of patients (N = 740; 73.5% represented by groups 1,2,3,6) would exhibit elevated levels in ≥2 biomarkers and over one-third of patients (N = 434, 43.1%) would concurrently demonstrate raised levels of EOS, FeNO and IgE.

In conclusion, based on the data from VOYAGE trial, 85.8% (N = 864) of paediatric patients with severe uncontrolled Type 2 asthma (100.0%-10.0%–4.2%) would meet the eligibility criteria for dupilumab treatment, exhibiting elevated blood EOS and/or increased FeNO levels.

Fig. 3 provides an overview of the dupilumab-eligible Italian patient population categorized by EOS and FeNO levels, with additional stratification based on the presence of allergic status (IgE≥100 IU/mL). Nearly half of the eligible patients (N = 454) would show elevated levels of both biomarkers, while the substantial majority (94.6%) would manifest at least an increase in EOS

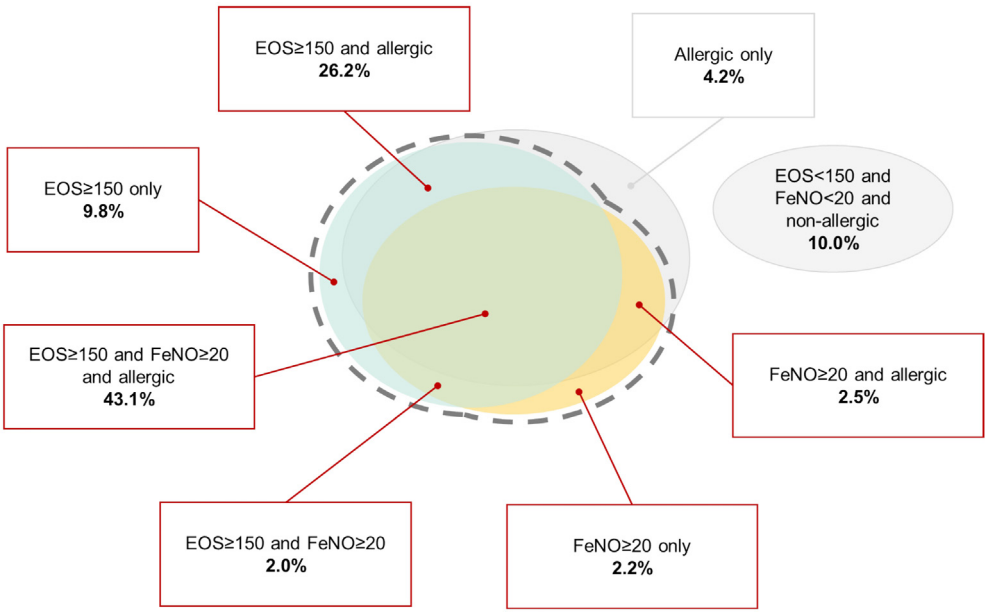

Fig. 2 Distribution of paediatric patients by Type 2 inflammation biomarkers [Elaborated from[6]]. *Allergic asthma definition: IgE≥100 IU/mL and at least 1 perennial allergen positive (≥0.35 IU/mL) for at least one aeroallergen-specific IgE at baseline. EOS: Eosinophils; FeNO: Fractional Exhaled Nitric Oxide.

#	Patient subgroup	Proportion of pts (%)	EOS≥150 cells/μL	FeNO≥20 ppb	IgE≥100 IU/mL[a]	Dupilumab-eligible	Number of eligible pts (N)
-	*All patients*	*100.0%*	*n/a*	*n/a*	*n/a*	*n/a*	*1007*
1	**EOS≥150 cells/μL** and FeNO<20 ppb and IgE≥100 IU/mL	26.2%	✓		✓	Yes	264
2	EOS<150 cells/μL and **FeNO≥20 ppb** and IgE≥100 IU/mL	2.2%		✓	✓	Yes	22
3	**EOS≥150 cells/μL** and **FeNO≥20 ppb** and IgE≥100 IU/mL	43.1%	✓	✓	✓	Yes	434
4	**EOS≥150 cells/μL** and FeNO<20 ppb and IgE<100 IU/mL	9.8%	✓			Yes	99
5	EOS<150 cells/μL and **FeNO≥20 ppb** and IgE<100 IU/mL	2.5%		✓		Yes	25
6	**EOS≥150 cells/μL** and **FeNO≥20 ppb** and IgE<100 IU/mL	2.0%	✓	✓		Yes	20
7	EOS<150 cells/μL and FeNO<20 ppb and IgE≥100 IU/mL	(4.2%)			✓	No	(42)
8	EOS<150 cells/μL and FeNO<20 ppb and IgE<100 IU/mL	(10.0%)				No	(101)
-	*All dupilumab-eligible patients*	*85.8%*	*n/a*	*n/a*	*n/a*	*Yes*	*864*

Table 2. Estimation of paediatric patients with severe uncontrolled asthma in Italy (> 2 exacerbations/year), characterized by Type 2 inflammation [Sources:[6]]. *EOS: Eosinophils; FeNO: Fractional Exhaled Nitric Oxide; IgE: Immunoglobulin E; n/a: Not available; pts: patients. [a]The assessment of IgE biomarker was conducted in the VOYAGE trial; however, IgE alone does not serve as a biomarker for determining eligibility for dupilumab. Dupilumab is specifically indicated in Type 2 asthma patients, identified by elevated blood eosinophils and/or increased fractional exhaled nitric oxide levels, irrespective of IgE concentrations*

levels (N = 817). Patients with elevated FeNO levels without a simultaneous increase in EOS would be less frequent (N = 47; 5.4% of the eligible population).

In total, 83.4% (N = 720) of the dupilumab-eligible patient population would also exhibit allergic status (ie, IgE≥100 IU/mL). Across all three subgroups, there would be a higher prevalence of allergic patients compared to non-allergic patients: 95.6% in the both EOS and FeNO raised group; 72.7% in the only EOS raised group; and 46.8% in the only FeNO group.

DISCUSSION

In the present study, we aimed to replicate the Canonica et al[12] analysis with the objective of assessing the epidemiological impact of severe asthma in the Italian paediatric population.

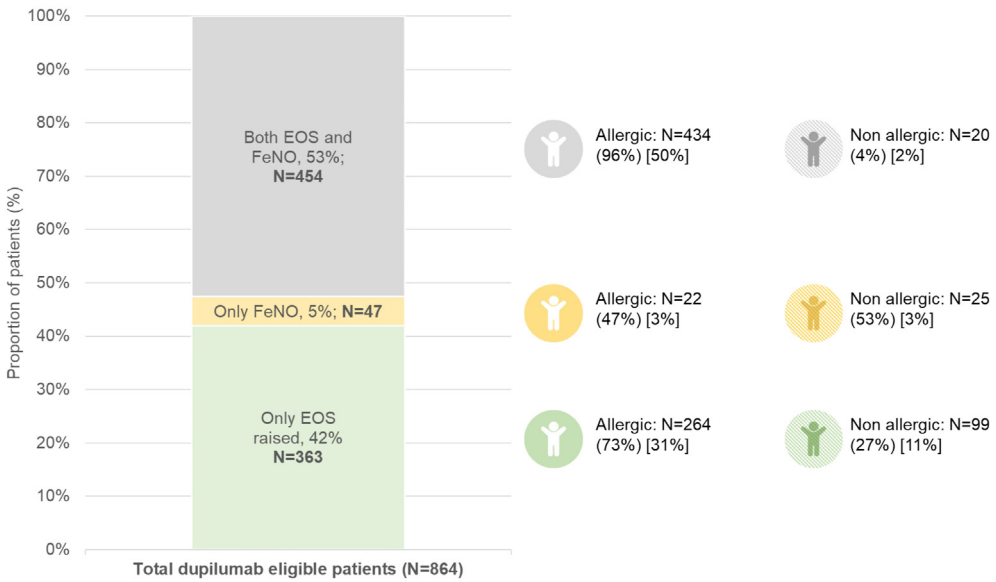

Fig. 3 Overview of estimated dupilumab-eligible patient population, in Italy. Percentage reported between round brackets (X%) refers to subgroup population. Percentage reported between square brackets [X%] refers to all dupilumab-eligible population. EOS: Eosinophils; FeNO: Fractional Exhaled Nitric Oxide.

Additionally, we sought to characterize the population by severity, nature of inflammation and anticipated distribution of biomarker levels.

Given the lack specific information pertaining to the paediatric population, we relied on the data from recent administrative database analysis focusing on adolescents and adults[14] as a valid reference to estimate the overall prevalence of asthma in children and the proportion of severe cases in Italy. While the general prevalence of asthma ranges approximately between 6% and 9% across children and adults,[8] it is noteworthy that only about 2% of this patient population holds an exemption code for asthma.[14] This implies that the remaining 4%–5% of patients likely have milder forms of asthma, not requiring the same high level of healthcare resources on a regular basis. Moreover, the number of hospital admissions for paediatric asthma can represent a valid and reproducible estimation of the severe cases, as well as an indicator of appropriateness and effectiveness of the assistance and management process of the subject affected by this pathology.[16]

In broad terms, the analyses indicated patients with severe uncontrolled asthma would constitute approximately 5% of all asthma patients undergoing regular follow-up (eg, spirometry) and about 11% of all actively treated asthma patients (eg, patients treated with ICS). These figures align closely with existing published literature, which suggests that severe asthma affects around 5%–10% of individuals with asthma. This subgroup is characterized by frequent exacerbations, regular use of high dose and frequent steroid administration, unscheduled healthcare visits, and a propensity for emergency room visits and hospitalization.[17–20]

The stratification of paediatric patients with uncontrolled asthma by biomarker levels was based on VOYAGE study outcomes.[6] This trial stands out as the sole randomized controlled trial (RCT) that recruited children between aged 6–11 years with moderate-to-severe asthma, regardless of minimum baseline blood EOS count or other Type 2 inflammation biomarkers. To our knowledge, the VOYAGE trial is a unique and comprehensive clinical study that provides a thorough overview of subpopulations of paediatrics asthmatic patients based on individual Type 2 biomarker levels (ie, raised EOS, FeNO or IgE) and combinations of these biomarkers (eg, patients with both increased EOS and FeNO level; patients with increased EOS and normal FeNO level, etc.). The distribution of children, by individual biomarker levels at baseline in the VOYAGE trial was consistent with the QUEST trial (a randomized, controlled by placebo trial assessing the efficacy of dupilumab in patients ≥12 years old with uncontrolled moderate-to-

severe asthma)[21] and the SANI (Severe Asthma Network in Italy) cohorts. The SANI registry, a national registry in Italy promoted by GINA Italy - SIAAIC (Società Italiana di Allergologia, Asma e Immunologia Clinica) and SIP (Società Italiana di Pneumologia), enrolled patients (age>12 years) with severe asthma in a real life setting.[18] For instance, the proportion of patients with EOS≥150 cells/μL was 81.1% in the VOYAGE trial (Table 2), 71.5% in the QUEST trial and 79.8% in the SANI registry, confirming EOS as the most prevalent biomarker among uncontrolled asthma patients. Similarly, 49.8% of patients had elevated FeNO levels (≥20 ppb) in the VOYAGE trial, 50.2% of patients had elevated levels (FeNO≥25 ppb) in the QUEST trial, and 50.1% of patients in the SANI registry.

According to our calculations, approximately one thousand children (aged 6–11 years) in Italy are living with severe uncontrolled asthma. Despite the relatively small number of children in this category, they contribute to around 50% of the healthcare costs associated with paediatric asthma.[22] Consequently, managing this group poses a significant challenge, requiring extensive diagnostic evaluation and leading to a substantial consumption of healthcare resources.[22]

Results of the present analysis showed that 864 patients (~86%), from a cohort with severe uncontrolled asthma with 2 or more exacerbations per year, have a Type 2 inflammation with raised EOS and/or FeNO levels, making them potentially eligible to dupilumab. Even if most of dupilumab-eligible patients demonstrate raised EOS level (N = 817, 95%), a non-negligible number of patients (N = 47, 5% of the eligible population) have increased FeNO levels without increased EOS.

These findings underline the significance of using a biomarker-driven approach in which clinicians would test peripheral-blood EOS counts, FeNO, or both to identify Type 2 asthma patients who are likely to benefit of treatments such as dupilumab.

It is plausible to presume that, there are a few methodological limitations in this analysis, that might increase uncertainty of the estimates and affect the validity of findings. First, there could be an underestimation of patients, because:

- We considered an administrative database analysis instead of clinical registry data, to estimate the paediatric population with uncontrolled asthma. Indeed, it is important to note that administrative databases typically do not capture patients who: i) see private care; ii) have intermittent disease, leading to temporary periods where they may not be recorded in the system but are likely to reappear later in time (severe refractory disease is estimated to occur in 5%–10% of all asthma patients[23,24]).
- The analysis was focused on the patient population with uncontrolled severe asthma, irrespective of therapy compliance. This approach carries the risk of including individuals with the highest medical needs while potentially excluding milder forms that may escalate in severity later on.

The estimate considered the patient population in treatment with high-dose ICS + LABA. As per EU label, severe asthma paediatric patients with medium dose treatment are also eligible to Dupilumab. Moreover, in clinical practice stepping up to high dose ICS for paediatrics is not common and does not bring efficacy benefit and potential side effects compared to be kept on medium dose ICS. Therefore, there is a probability that such a methodology could lead to an underestimation of the eligible population. Nevertheless, we trust that this estimate remains more precise and accurate than registry-based assessments, which often rely on much smaller sample sizes and have a tendency to overestimate eligible patients.

A second limitation of the analysis consist of the use of clinical trial data (ie, VOYAGE) to stratify the asthma population by biomarker levels. The selection of VOYAGE data was required due to the absence of real-world Italian data, but it may not fully represent of the local situation. However, comparisons with the QUEST and SANI cohorts demonstrated a reasonable level of consistency between the sources, supporting the methodological appropriateness of our choice. Caution should be exercised when extrapolating these findings to the broader "severe" paediatric asthma population, particularly considering the possibility of a higher prevalence of patients with low eosinophil counts in clinical practice than what was represented in the VOYAGE study. Indeed,

significant changes might occur if the analysis were conducted on real clinical data in 2024.

In conclusion, we successfully estimated the number of paediatrics patients who might eventually be eligible for dupilumab in Italy, utilizing data on clinical assessment and biomarker testing from the VOYAGE trial (EOS and/or FeNO, N = 864, 85.8% of patients with severe uncontrolled asthma). Literature data[6] showed that children treated with dupilumab exhibited a high response rate. At week 52, the response rates were 86% vs 75% with placebo (*OR: 2.57;* p = 0.0051). This trend persisted even among patients characterized by baseline blood EOS≥300 cells/μL (at week 52, 87% vs 81%; *OR: 3.67;* p = 0.0009). It is essential and strongly advised to conduct testing for multiple biomarkers concurrently during baseline patient assessment and disease follow-up. Relatively low-cost tests allow physicians to determine the number of patients with severe asthma and Type 2 inflammation, categorize them into phenotypes (eosinophilic, allergic, or mixed), and subsequently identify and prescribe the most suitable therapy while evaluating the need for treatment adjustments.

Abbreviations

EOS, Eosinophils; **FeNO**, Fraction of exhaled nitric oxide; **GINA**, Global Initiative for Asthma; **ICS**, Inhaled Corticosteroids; **IgE**, Immunoglobulin E; **IL**, Interleukin; **ISTAT**, Italian Institute of Statistics; **LABA**, Long acting beta-agonists; **SANI**, Severe Asthma Network in Italy; **SIAAIC**, Società Italiana di Allergologia, Asma e Immunologia Clinica; **SIDRIA**, Studi Italiani sui Disturbi Respiratori dell'Infanzia e l'Ambiente; **SIP**, Società Italiana di Pneumologia.

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Statement of contribution to the work

All authors contributed to idealizing the design of the study.
BR, FG, and FF conceptualized the analysis, and evaluated results.
All authors reviewed the content of the analysis (methods and results) and approved it.
BR, FG, and FF drafted the first version of the manuscript.
All authors contributed to the refinement of the manuscript.
All authors read and approved the final manuscript.

Ethics statement

This study is exempted from Institutional Review Board (IRB) approval as the epidemiological analysis was based on literature and publicly available data.

Agreement to publish the work

All authors consent to publication.
This manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

Declaration of competing interest

R. Cutrera received personal fees from Astra Zeneca, Sanofi, Fidia and GSK; G. Marseglia received personal fees from Aboca; M. Miraglia del Giudice received personal fees from Eurospital, Bayer, Noos, Deca and Reckitt Benckiser; G. Piacentini received personal fees from Sanofi, Regeneron, Chiesi, GSK, Noos, Angelini, Recordati, Novartis and Microfarma; A. Stassaldi, G. Nicolosi, F. Fanelli are Sanofi employees and may hold shares and/or stock options in the company. R. Bitonti and G. Furneri are employees of PharmaLex Italy. PharmaLex Italy received consulting fees from Sanofi for conducting the analysis. The rest of the authors declare that they have no relevant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100933.

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