

ORIGINAL ARTICLE

Airways Disease

Mechanical bacterial lysate administration prevents exacerbation in allergic asthmatic children—The EOLIA study

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Abstract

Background: Despite progress in asthma management, prevention of asthma exacerbation remains challenging in school-aged children with allergic asthma. New therapeutic approaches are needed. Previously, a chemical bacterial lysate has been successfully used in preschool children to reduce wheezing attacks. We assessed the effect of Polyvalent Mechanical Bacterial Lysate (PMBL[®]) Tablet on asthma clinical course and control in 6- to 16-year-old children with partly controlled or uncontrolled allergic asthma.

Methods: A randomized, double-blind, placebo-controlled, parallel-group study was performed in 152 patients exhibiting allergic asthma assigned to receive Placebo or PMBL[®]. Eligible patients underwent four visits during the 9-month study. Asthma control level was assessed by ACT/C-ACT score.

Results: The main criterion was not achieved as ACT/C-ACT changes were similar in both groups at the end of the 3-month treatment period. However, the mean number ($\pm$ SD) of asthma exacerbations was significantly lower with PMBL[®] Tablet than with Placebo at Week 12 (0.3 ± 0.6 vs 0.8 ± 1.1 , $P = .009$) and over the total study period (1.1 ± 1.3 vs 1.9 ± 2.0 , $P = .01$). Consistently, the mean number of days with exacerbation per patient was significantly lower with PMBL[®] Tablet (13.3 ± 11.2 vs 19.8 ± 15.7 over the whole study, $P = .009$). Treatment with PMBL[®] Tablet prolonged the time to second exacerbation by 55% (Hazard Ratio [HR]=0.45; 95% Confidence Interval [CI] 0.27 to 0.77, $P = .002$) and to third exacerbation by 74% (HR=0.26; 95% CI 0.12 to 0.58, $P < .001$). No serious adverse event related to PMBL[®] Tablet administration was recorded.

Conclusion: Administration of PMBL[®] Tablet represents a safe and effective means for significantly reducing the rate of exacerbations in school-aged allergic asthmatic children. (EudraCT 2013-000737-12 and NCT02541331)

KEYWORDS

allergic asthma, children, exacerbation, PMBL[®] Tablet

1 | INTRODUCTION

Asthma is the most common chronic respiratory disease in children.^{1,2} The natural course of asthma includes episodic exacerbations with worsening in symptoms. Asthma exacerbations

and their associated costs have a significant clinical and societal impact.³⁻⁵

Respiratory infections and allergens are both involved in the onset of asthma exacerbation in children with allergic asthma.⁶ In particular, the role of viral respiratory infections, and to a lesser

extent of bacterial infections, in producing acute exacerbations is well established.⁷⁻⁹ Furthermore, previous studies have demonstrated that concurrent viral illness and allergic sensitization increase the likelihood of asthma exacerbations and hospitalizations due to severe symptoms.^{10,11}

The long-term goals of asthma management are to achieve satisfactory symptom control and to minimize the risk of exacerbations, fixed airflow limitation, and the side effects of treatment.¹² Despite progress in asthma management, prevention of exacerbations remains challenging in children with persistent asthma.⁴

Polyvalent Mechanical Bacterial Lysate (PMBL®) Tablet has been widely used since 1995 to prevent acute and recurrent infections of upper and lower respiratory tract in adult and pediatric populations. It is administered via the sublingual route and is well tolerated.¹³ The mechanism of action of PMBL® starts with the maturation of different dendritic cells subsets, followed by a synergic activation of T and B cells that results in the secretion both at systemic and locoregional level of antibodies specific for antigen administered.¹⁴ Although less studied, the ability of PMBL® to reduce viral infection is also reported.¹⁴

A close association between allergic airway disease and virus-induced exacerbation of asthma is well established, suggesting that controlling allergic inflammation and enhancing antiviral responses might be effective approaches to reducing the frequency and severity of asthma exacerbation.¹⁵

A positive clinical effect of PMBL® has been shown in children and adults with allergic rhinitis.¹⁶ Moreover, reduction of number and duration of wheezing attacks in children with a chemical bacterial lysate (OM-85 BV) has been demonstrated.¹⁷ This study reported a reduction of respiratory tract infections which was most likely considered to explain the reduction in wheezing attacks. The authors speculated that OM-85 BV-mediated increase in INF γ (Th1-associated cytokine) could explain its benefit. A reduction of the frequency of asthma attacks and use of antibiotics have also been observed in children treated with OM-85 BV as add-on therapy to ICS as compared to the group treated with ICS alone.¹⁸ Based on the number of natural killer T cells and their cytokine production, the authors suggested that OM-85 BV could preferentially restore Th1 response which is altered in children with asthma.

On the other hand, epithelial cells at mucosal surfaces might also directly sense pathogen-associated molecular patterns (PAMPs), which are contained in PMBL®, and react by augmenting their barrier function, signaling to leukocytes, and directly killing pathogens, thus further contributing to prevention of infections.¹⁹

In this context, we hypothesized that treatment with PMBL® Tablet could improve asthma course and control in school-aged children with persistent allergic asthma. The respiratory tract of this population is exposed to the cumulative effects of air pollution and allergens, cold weather and school promiscuity which together confer a high risk of contracting viral and bacterial respiratory infections.

2 | METHODS

2.1 | Patients

Eligible participants were (i) children (aged 6 to 16 years) diagnosed with asthma according to the Global Initiative for Asthma (GINA) 2012 guidelines¹² (ii) with perennial sensitization to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* allergens defined as a positive skin prick test (Allergopharma-Nexter Sp. z o.o.- Poland) with wheal diameter ≥ 3 mm and greater than negative control or allergen-specific IgE level $\geq$ class 2 (Polycheck®, Biocheck-GmbH, EMMA-MDT Sp. z o.o.- Poland), (iii) showing clinical characteristics of partly controlled or uncontrolled asthma and treated according to GINA¹² and (iv) with experience of at least two asthma exacerbations in the previous year. All study patients were recruited between mid-July and end of September to allow stimulation of the immune system prior to the onset of seasonal viral attacks.

2.2 | Study design

This study (Efficacy Of mechanical bacterial Lysate In Allergic children, EOLIA Study) was a randomized, double-blind, placebo-controlled, parallel-group study. The study was conducted in four sites in Poland between July 2014 and June 2015.

The primary study objective was to assess the efficacy of PMBL® Tablet in improving asthma control level following 3 months use as an add-on therapy to routine asthma treatment. Improvement was assessed via the Childhood-Asthma Control Test (C-ACT) (for children <12 years, caregiver and child, self-reported) and the Asthma Control Test (ACT) (for children ≥ 12 years, self-administered) score.

The secondary objectives were (i) to assess the effects of PMBL® Tablet (vs Placebo) on the number of respiratory tract infections during the study period, (ii) to assess the reduction (vs Placebo) of the number of asthma exacerbations, (iii) to assess the times (vs Placebo) to first, second and third exacerbation, (iv) to compare the mean number of days of short-acting β_2 -agonists (SABA) use for relief of exacerbation over the whole study period.

The randomization list was generated by a statistical services company (Statitec, 31670 Labège, France) using a standard SAS routine (SAS Institute Inc., Cary, NC 27513).

The study protocol was approved by the Bioethics Committee of the Medical University of Lublin and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from parents of patients before enrollment in the study, and a signed assent was obtained from all patients.

2.3 | Interventions

PMBL® Tablet (Ismigen®, Lallemand Pharma AG, Massagno, Switzerland) contains 7 mg of bacterial lysate from the following bacteria: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus (viridans) oralis*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Haemophilus*

influenzae Serotype B, *Neisseria catarrhalis*, and *Streptococcus (Diplococcus) pneumoniae* (six strains).

Patients received one tablet per day before breaking fast, on the first 10 days of each month, for three consecutive months. The threshold for product compliance was set to 80% of total treatment.

2.4 | Study protocol

The protocol included four visits: a Screening/Randomisation visit ("Baseline"), an end-of-treatment visit (at Week 12), and two follow-up visits (at Week 24 and Week 36). Patients recorded their asthma symptoms, use of reliever medication, episodes of infections, and exacerbations in a diary. Exacerbations were assessed and validated by the investigator on the basis of deterioration in symptoms and temporary change in treatment.^{20,21}

Severity of asthma exacerbations was defined as:

1. Mild/moderate if requiring a transient increase in ICS/ β_2 -agonists/anticholinergic use for ≥ 2 days, or an emergency room visit but without prescription of systemic corticosteroids.
2. Severe if requiring hospitalization or emergency room visit and systemic corticosteroids to be prescribed or systemic corticosteroids (oral or parenteral) to be prescribed for ≥ 3 days but < 7 days.

Exacerbations were recorded as "related to infection" when occurring during an infection and as "unrelated to infection" in

the absence of clinical symptoms of infection. Acute respiratory tract infections were diagnosed and reported according to clinical practice.

2.5 | Statistical analysis

Based on the literature and clinical experience, a difference of 1.8 points in the primary outcome measure (ie, mean C-ACT or ACT score) between PMBL[®] Tablet and Placebo was considered clinically relevant.²⁰⁻²²

The sample size was calculated using the POWER procedure (SAS). A total of 64 evaluable patients per group were to be enrolled to ensure a power of 85% to detect the abovementioned group difference, with an α level of 0.05, and standard deviations (SD) equal to 3.2 for PMBL[®] Tablet and 3.5 for Placebo. The total sample size calculation required to enroll 150 patients in anticipation of a drop-out rate of 15%-20%.

Efficacy analyses were performed on the Full Analysis Set (FAS) population ($n = 150$). All safety parameters were summarized in the Safety Set ($n = 151$).

Between-group comparisons of the mean change in C-ACT or ACT scores between Baseline and subsequent study visits were performed using analysis of covariance (ANCOVA), with Baseline score as a covariate. In the case of non-normal distribution of scores (assessed by Shapiro-Wilk test), a nonparametric ANCOVA based on ranks was used. Comparisons of the mean number of respiratory

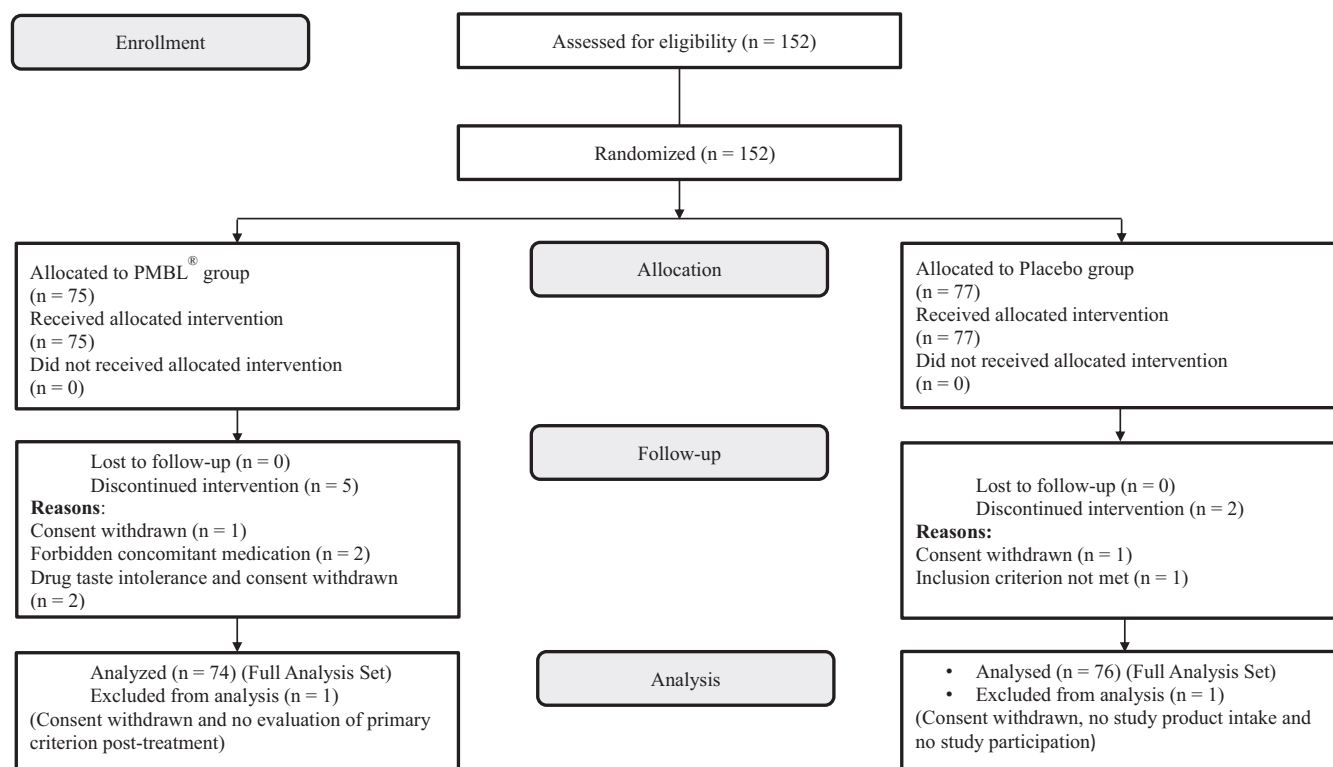


FIGURE 1 Study flowchart. Progression of study participants through the study, presented as per the Consolidated Standards of Reporting Trials (CONSORT) guidelines. In this evaluation, the Full Analysis Set included all patients having at least one evaluation of the primary criterion after treatment start. PMBL - Polyvalent Mechanical Bacterial Lysate

infections and asthma exacerbations, mean number of days with asthma exacerbation, and mean number of days of SABA use were performed using Student's *t* test or Wilcoxon's test in the case of non-normality. Categorical variables were compared using chi-square test or Fisher's exact test. The cumulative survival rates (ie, the period without exacerbation, and the times to first, second, and third asthma exacerbations) were estimated using a survival analysis (Kaplan-Meier). The SAS life-test procedure was used to compute nonparametric estimates of the length of event-free periods by the Kaplan-Meier method. Comparison between these functions was made using log-rank tests. All *P* values were 2-tailed; a *P* value of less than .05 was considered statistically significant.

3 | RESULTS

A total of 152 patients were screened and randomized in the study. Five patients in the PMBL[®] Tablet group and two in the Placebo group did not complete the study (Figure 1).

Compliance (mean %±SD) to the study treatment in the Safety Set was similar in both groups: 97.16 ± 14.68 and 99.74 ± 1.42 in the PMBL[®] Tablet and Placebo groups, respectively. No patient diary was missing. Main demographic characteristics and history of exacerbations and respiratory tract infections were comparable in both groups (Table 1). The asthma severity was not assessable at Baseline because most participants in the EOLIA study had uncontrolled symptoms at entry. Likewise, the immunological status was not investigated in detail in all patients.

The primary end-point was not reached (Table 2). The absolute change in C-ACT and ACT scores between Baseline and Week 12 was comparable between groups. A similar trend was observed at the Week 24 and Week 36 time-points.

More than 60% of the infections reported during the study period were common cold and pharyngitis, irrespective of treatment group (data not shown). No significant difference was observed between groups in the mean number of respiratory tract infections per patient. In contrast, the number of patients with at least one infection leading to asthma exacerbation was significantly reduced after treatment with PMBL[®] Tablet (Table 3).

The mean number of asthma exacerbations was 63% lower with PMBL[®] Tablet than with Placebo at Week 12 (*P* = .009), and the reduction was 42% over the whole study period (*P* = .01) (Table 4). Consistent with this, the mean number of days with exacerbation was 33% lower with PMBL[®] Tablet across the study (*P* = .009), and the mean number of days of SABA use for exacerbation relief per patient was 26% lower (*P* = .02 vs Placebo). In both groups, the majority of exacerbations were classified as mild/moderate (94.9% and 98.6% in the PMBL[®] Tablet and in the Placebo groups, respectively). PMBL[®] Tablet reduced by 50% (*P* = .03 vs Placebo) the mean number of asthma exacerbations related to infections per patient at Week 12 and by 44% (*P* = .005) over the whole study period (Table 4). With regard to exacerbations unrelated to infections, no preventive effect of PMBL[®] Tablet was found. A borderline significant reduction

TABLE 1 Demographic characteristics, asthma treatments, and history of asthma exacerbations and infections in the study population—Full Analysis Set (*n* = 150)

	PMBL [®] Tablet	Placebo	<i>P</i> -value
Age ^a (y)	9.3 (2.7)	9.8 (2.6)	.23
Age in class, <i>n</i> (%)			
<12 y	56 (75.7)	54 (71.1)	-
≥12 y	18 (24.3)	22 (28.9)	-
Sex, <i>n</i> (%)			
Male	49 (66.2)	57 (75.0)	.24
Female	25 (33.8)	19 (25.0)	
Weight ^a (kg)	39.3 (16.3)	40.5 (15.7)	.64
Time since diagnosis of asthma ^a (y)	4.7 (3.2)	5.0 (3.4)	-
Asthma exacerbation unrelated to infection ^a (past year)	2.3 (1.8)	2.1 (1.4)	.89
Current asthma treatment at inclusion, <i>n</i> (%)			
ICS + LABA	42 (56.8)	42 (55.3)	-
ICS	32 (43.7)	34 (44.7)	-
Asthma exacerbation related to infection ^a (past year)	2.5 (1.3)	2.4 (1.3)	.61
Number of acute respiratory infections ^a (past year)	3.9 (1.3)	4.0 (1.9)	.98
C-ACT score ^a	16.5 (2.5)	16.8 (2.6)	1.00
ACT score ^a	17.8 (1.7)	17.0 (1.9)	.05

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; PMBL, Polyvalent Mechanical Bacterial Lysate; SD, standard deviation.

^aMean (SD).

was observed at Week 12, however, potentially suggestive of some treatment effect (Table 4).

The Kaplan-Meier plots presented in Figure 2 illustrate the time to occurrences of asthma exacerbation in the two treatment groups. The time to first asthma exacerbation (ie, event-free time) was prolonged by 30% in the PMBL[®] Tablet group vs Placebo group (hazard ratio [HR]: 0.70; 95% confidence interval [CI] 0.46 to 1.06, *P* = .09), although not statistically significant (Figure 2A). This trend was confirmed for time to second and third occurrences of asthma exacerbation, both of which were significantly prolonged in the PMBL[®] Tablet group: by 55% (HR=0.45; 95% CI 0.27 to 0.77, *P* = .002) and by 74% (HR=0.26; 95% CI 0.12 to 0.58, *P* < .001), respectively (Figure 2B,C).

No serious adverse reactions were reported. One patient in the PMBL[®] Tablet group reported an adverse drug reaction of

	PMBL® Tablet	Placebo	P-value
C-ACT score			
Week 12 ^a	21.0 (3.3) (n = 56)	21.7 (2.6) (n = 52)	.227
Week 24 ^a	22.4 (3.6) (n = 56)	22.4 (3.4) (n = 51)	.927
Week 36 ^a	23.2 (2.6) (n = 54)	23.1 (3.2) (n = 45)	.893
ACT score			
Week 12 ^a	20.9 (4.3) (n = 18)	20.0 (3.5) (n = 24)	.278
Week 24 ^a	22.0 (3.4) (n = 18)	22.2 (2.5) (n = 25)	.930
Week 36 ^a	22.3 (2.8) (n = 20)	21.3 (3.1) (n = 31)	.213
ACT/C-ACT changes vs baseline			
Week 12 vs Baseline	4.0 (3.7) (n = 72)	4.3 (3.1) (n = 76)	.90
Week 24 vs Baseline	5.4 (3.5) (n = 71)	5.6 (3.5) (n = 75)	.69
Week 36 vs Baseline	6.1 (3.3) (n = 70)	5.6 (3.2) (n = 75)	.20

ACT, Asthma Control Test; C-ACT, Childhood Asthma Control Test; PMBL, Polyvalent Mechanical Bacterial Lysate; SD, standard deviation.

^aMean (SD).

TABLE 3 Mean number of respiratory infections and number of patients with at least one infection leading to exacerbation—Full Analysis Set (n = 150)

	PMBL® Tablet	Placebo	P-value
Mean number of respiratory infections			
Baseline-Week 12 ^a	0.7 (0.8) (n = 72)	0.7 (0.9) (n = 76)	.71
Week 12-Week 24 ^a	0.5 (0.7) (n = 71)	0.6 (0.8) (n = 75)	.37
Week 24-Week 36 ^a	0.8 (0.9) (n = 70)	0.7 (0.8) (n = 75)	.95
Baseline-Week 36 ^a	1.9 (1.7) (n = 74)	2.0 (1.8) (n = 76)	.96
Number of patients with at least one infection leading to asthma exacerbation (0-36 wk)	10	21	.002

PMBL, Polyvalent Mechanical Bacterial Lysate; SD, standard deviation.

^amean (SD).

"drowsiness" during the three treatment cycles. However, its intensity was reported to be mild and did not lead to treatment discontinuation.

4 | DISCUSSION

The primary end-point assessing the potential of PMBL® Tablet to improve the asthma control level of treated patients relative to Placebo was not achieved. Moreover, PMBL® Tablet and Placebo groups could not be discriminated by their C-ACT and ACT scores, although PMBL® Tablet treatment reduced the mean number of asthma exacerbations. The improvement of asthma control status based on C-ACT and ACT scores in both treatment groups was

TABLE 2 Childhood Asthma Control Test and Asthma Control Test—Full Analysis Set (n = 150)

unexpected. However, it is recognized that participation in a clinical study may improve asthma control, even in patients who receive Placebo.^{1,23} Furthermore, as recently highlighted by the European Respiratory Society Task Force, C-ACT and ACT questionnaires address the four preceding weeks and do not take into account exacerbations if not in the recall window of the questionnaires.²⁴ This could explain why the C-ACT and ACT scores were not significantly different between groups at any study time-point.

PMBL® Tablet treatment did not reduce the mean number of respiratory tract infections when compared to Placebo treatment. However, the present study was not designed to demonstrate an effect of PMBL® Tablet on infections. Indeed, around 70% of patients did not display a history of recurrent infections at Baseline. Due to the low rate of respiratory tract infections in the EOLIA study population, the statistical power of the study was not sufficient to address this end-point.

The most important finding in the study is the reduced rate of asthma exacerbations in the PMBL® Tablet group, with a parallel decrease in SABA consumption for exacerbation relief. Moreover, this reduction translated into a prolonged event-free time preceding occurrence of second and third episodes of exacerbation.

Although daily use of ICS is known to reduce asthma attacks, the lower number of exacerbations observed in the present study with PMBL® Tablet cannot be attributed to the ICS (± LABA) treatment since mean daily doses of ICS over the whole study period were comparable in both groups.

The preventive action of PMBL® Tablet on exacerbations related to infection appeared to be more pronounced than the effect on exacerbations unrelated to infection. However, the number of exacerbations unrelated to infections was lower than the number of exacerbations related to infections at Week 12, which could impact the statistical power of the analysis. Thus, it is hard to speculate about a specific effect for PMBL® Tablet in reducing asthma exacerbations related to infection. Most likely the preventive effect is more

TABLE 4 Asthma exacerbations, use of short-acting β_2 -agonists for exacerbation relief, mean daily doses of ICS during the study—Full Analysis Set (n = 150)

	PMBL [®] Tablet	Placebo	P-value
Mean number of asthma exacerbations per patient			
Baseline-Week 12 ^a	0.3 (0.6) (n = 72)	0.8 (1.1) (n = 76)	.009
Week 12-Week 24 ^a	0.4 (0.7) (n = 71)	0.6 (0.9) (n = 75)	.17
Week 24-Week 36 ^a	0.4 (0.7) (n = 70)	0.6 (1.1) (n = 75)	.44
Baseline-Week 36 ^a	1.1 (1.3) (n = 74)	1.9 (2.0) (n = 76)	.01
Mean number of days with exacerbations per patient			
Baseline-Week 36 ^a	13.3 (11.2) (n = 42)	19.8 (15.7) (n = 49)	.009
Mean number days of SABA use for exacerbation relief per patient during the study ^a	11.5 (11.2) (n = 37)	15.6 (10.2) (n = 47)	.02
Mean number of asthma exacerbations related to infection			
Baseline-Week 12 ^a	0.2 (0.5) (n = 72)	0.4 (0.8) (n = 76)	.03
Week 12-Week 24 ^a	0.1 (0.4) (n = 71)	0.2 (0.6) (n = 75)	.13
Week 24-Week 36 ^a	0.2 (0.5) (n = 70)	0.3 (0.7) (n = 75)	.27
Baseline-Week 36 ^a	0.5 (0.9) (n = 74)	0.9 (1.2) (n = 76)	.005
Mean number of asthma exacerbations per patient unrelated to infection			
Baseline-Week 12 ^a	0.1 (0.3) (n = 72)	0.3 (0.7) (n = 76)	.06
Week 12-Week 24 ^a	0.2 (0.5) (n = 70)	0.3 (0.7) (n = 75)	.27
Week 24-Week 36 ^a	0.2 (0.5) (n = 70)	0.3 (0.8) (n = 75)	.92
Baseline-Week 36 ^a	0.6 (0.7) (n = 74)	1.0 (1.5) (n = 76)	.41
Mean daily dose of ICS used over the whole study period (beclomethasone equivalent)	283 $\pm$ 107 μ g (n = 74)	289 $\pm$ 118 μ g (n = 76)	P = .795

ICS, inhaled corticosteroids; PMBL, Polyvalent Mechanical Bacterial Lysate; SABA, short-acting β_2 -agonists; SD, standard deviation.

^aMean (SD).

general and relates to both infection-related and infection-unrelated episodes.

Asthma exacerbations are an exaggerated response of lower respiratory airways to an environmental exposure. In children with established asthma, a vast majority of asthma exacerbations are

related to a viral illness mainly caused by rhinovirus.^{7-9,25,26} Although the underlying mechanisms are not completely understood, a growing body of evidence supports the view that viral infection and allergy interact to increase the risk and the severity of exacerbation,^{1,8,26} with respiratory allergies somehow inhibiting antiviral defenses.^{7,15,26}

Interestingly, the majority of infections from allergic patients of EOLIA study appeared to be common cold and pharyngitis, which are mostly due to viral agents, although coinfection with bacterial pathogens cannot be excluded.

Thus, we currently favor the idea that besides the adaptive immune response against bacterial products, innate mechanisms of immune protection, mediated by both innate lymphocytes and epithelial cells, might be triggered by bacterial lysates exposing PAMPs.^{19,27-29} The activation of these innate immune barriers, involving also type 2 and type 3 innate lymphoid cells (ILC), would also play relevant roles in tissue reparation upon viral and/or bacterial infections, thus limiting the duration and magnitude of airway tissue inflammation.^{30,31} Another interesting hypothesis can rely on the activation of T regulatory cells upon a long-term bacterial lysate administration, which might resemble a chronic infection. Also, as IL-10 and TGF β represent cytokines abundantly released at mucosal surfaces by accessory myeloid cells upon recognition of PAMPs, a locoregional expansion and/or activation of T regulatory cells (Treg) can be envisaged. Treg might eventually control Th2 response therefore further contributing to the amelioration of asthma status. Nevertheless, further studies are now clearly required to shed light on the fine immunological mechanisms triggered by PMBL[®].

Only a few studies investigating the impact of bacterial lysates on the clinical course of asthma in children are available.^{17,18} The most relevant study was performed by Razi and colleagues with OM-85 BV. This study reported a reduction of respiratory tract infections which was considered to be most likely to explain the observed reduction in wheezing attacks.¹⁷ Our results differ from these observations. Although it might be difficult to speculate regarding these different results, it ought to be noted that in the former study, the studied population was comprised of preschool children mostly non-atopic, exhibiting a history of recurrent respiratory infections and persistent asthma in 31% patients only. Furthermore, administration of inhaled or systemic corticosteroids was prohibited within the month prior to enrollment.

The mechanism of action of PMBL[®] Tablet on asthma exacerbations remains to be further investigated as it could impact its current therapeutic paradigm. Indeed, if it were to be demonstrated that the reduction of exacerbation number by PMBL[®] Tablet was mediated through a non-specific, anti-inflammatory action and improved tissue reparation capabilities, it could be pertinent to extend PMBL[®] Tablet intake beyond its currently recommended usage. Moreover, although no autoimmunity development compared to Placebo has been observed in children with sporadic IgA deficiency treated by a bacterial lysate within a four-year follow-up period,³² it would be valuable to investigate long-term outcomes in immunocompetent or immunodeficient

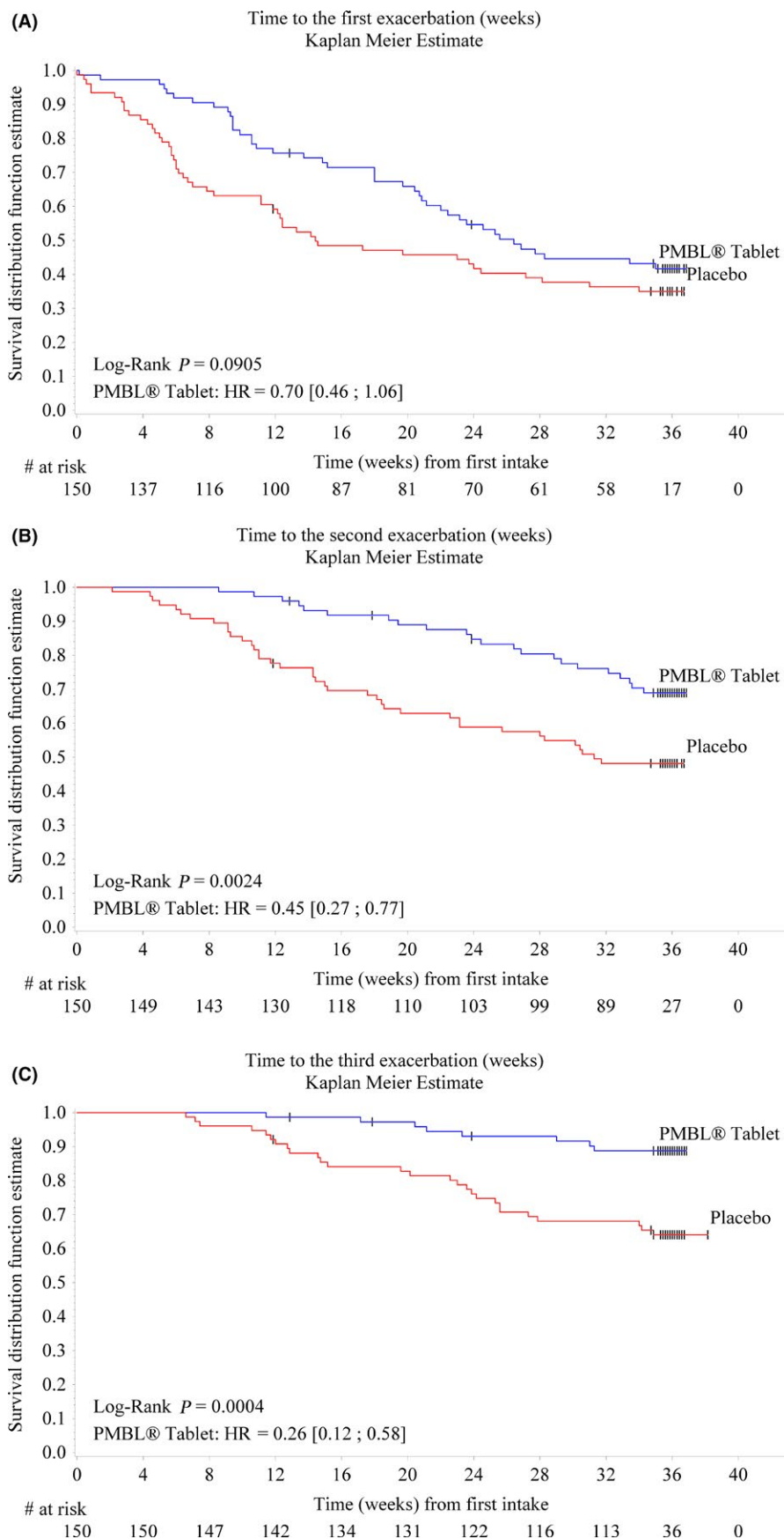


FIGURE 2 Time to reach asthma exacerbations. The time taken to reach the first, second, and third asthma exacerbations by both study groups is illustrated in Figure 2A-C, respectively. HR, Hazard Ratio

children. The impact of asthma severity on PMBL[®] Tablet activity in preventing asthma exacerbation should also be studied.

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CONFLICT OF INTEREST

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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