EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2019
EMA/457345/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Bacterial lysates-containing medicinal products for respiratory conditions

Active substances:

Haemophilus influenzae / klebsiella pneumoniae / moraxella catarrhalis / staphylococcus aureus / streptococcus mitis / streptococcus pneumoniae / streptococcus pyogenes,

Haemophilus influenzae / klebsiella pneumoniae / moraxella catarrhalis / staphylococcus aureus / streptococcus pneumoniae / streptococcus pyogenes,

Streptococcus pneumoniae / streptococcus agalactiae / staphylococcus aureus / haemophilus influenzae,

Haemophilus influenzae / klebsiella ozaenae / klebsiella pneumoniae / moraxella catarrhalis / staphylococcus aureus / streptococcus pneumoniae / streptococcus pyogenes / streptococcus viridans,

Haemophilus influenzae / membrane fraction of klebsiella pneumoniae / ribosomal fractions of klebsiella pneumoniae / streptococcus pneumoniae / streptococcus pyogenes,

Escherichia Coli/ Klebsiella Pneumoniae / Staphylococcus Aureus / Staphylococcus Epidermidis / Streptococcus Salivarius / Streptococcus Pneumoniae/ Streptococcus Pyogenes / Haemophilus Influenzae / Corynebacterium Pseudodiphtheriticum / Moraxella Catarrhalis

Procedure number: EMEA/H/A-31/1465

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Bacterial lysates-based medicinal products are authorised in various indications including the prevention and/or treatment of different types of respiratory infections. The Italian National Competent Authority (AIFA) considered that results of recent studies cast doubt on the efficacy of these products in respiratory infections. Therefore, and taking into account the known very rare risk of serious immunological reactions associated to these products, AIFA considered it to be in the interest of the Union to review the impact of these concerns on the benefit-risk balance of the class of bacterial lysates-based products in their authorised indications for respiratory infections.

On 8 June 2018 the Italian National Competent Authority (AIFA) therefore triggered a referral under Article 31 of Directive 2001/83/EC and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of bacterial lysates-containing medicinal products for respiratory conditions and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

The scope of this procedure is limited to respiratory tract conditions.

2. Scientific discussion

2.1. Introduction

Bacterial lysates-based medicinal products (hereinafter referred to as “bacterial lysates”) are classified as bacterial vaccines or immune-stimulating agents depending on European Union Member States (EU MSs). These medicinal products contain several strains of inactivated whole bacteria/bacterial lysates/bacterial fractions claimed to stimulate the immune system to recognise and fight infections. These medicines are available for oral use (capsules, tablets, granules/powder for oral solution or drops), sublingual use (sublingual tablets), nasal use (drops for inhalation) or intramuscular/subcutaneous use (suspension for injection). Their mechanism of action has been investigated in recent years, but their role in immune response triggering is not fully elucidated. The most plausible explanation is an IgA antibody response against pathogens at mucosal surfaces and activation of mucosal dendritic cells by Toll-Like Receptor (TLR)-dependent signaling through TLR-2/6 and TLR-9 (Kearney, 2015). Eight medicinal products containing six different combinations of bacterial strains’ lysates currently hold marketing authorisations. Their respective indications differ across MS and can be summarised as follows:

- *Haemophilus influenzae / klebsiella pneumoniae / moraxella catarrhalis / staphylococcus aureus / streptococcus mitis / streptococcus pneumoniae / streptococcus pyogenes*, commercialised as Luivac (and associated name Paspat) is authorised in 11 MS as tablets for the prophylaxis of recurrent respiratory tract infections (RRTI) in adults and children from 4 years of age. In one MS, the paediatric indication is restricted to recurrent upper RTI (RURTI).
- *Haemophilus influenzae / klebsiella pneumoniae / moraxella catarrhalis / staphylococcus aureus / streptococcus pneumoniae / streptococcus pyogenes* commercialised as

  Respivax authorised in one Member State (MS) as tablets for prophylactic and therapeutic treatment of chronic and recurrent RTI in adults and children from 3 years of age, and

  Lantigen B authorised in four MS, as oral drops for prophylactic and therapeutic treatment of RURTI or bacterial URTI in adults and children in two MS, as prophylaxis of RRTI in adults and

URTIs in children in a third MS and in the fourth MS for the prevention of RRTI in adults and children from 3 years of age.

- *Streptococcus pneumoniae / streptococcus agalactiae / staphylococcus aureus / haemophilus influenzae* commercialised as Buccalin authorised in two MS as film coated tablets, for the prophylaxis of RRTI in adults and of bacterial RURTI in children older than 6 months in one MS and in the other for the prophylaxis of bacterial RTI without age limits.
- *Haemophilus influenzae / klebsiella ozaenae / klebsiella pneumoniae / moraxella catarrhalis / staphylococcus aureus / streptococcus pneumoniae / streptococcus pyogenes / streptococcus viridans (oralis or sanguinis)* commercialised as

  Ismigen (and associated names Immubron, PIR-05 and Provax), for which the viridans streptococcal species is streptococcus oralis, which is manufactured by mechanical lysis and is authorised in four MS as sublingual tablets for the prophylaxis of RRTI in adults. In two of these MS it is also authorised for the treatment of acute, subacute recurrent or chronic RTI and in one in children from 3 years of age.

  Broncho-vaxom (and associated names Broncho-Munal and Ommunal), for which the viridans streptococcal specie is streptococcus sanguinis, which is a lyophilised bacterial lysates authorised in sixteen MS as capsules for the prevention and treatment of RRTI in adults and children. In one MS the indication in children is limited to bacterial RURTI, while in five others it is also generally authorised as immunotherapy. Depending on MS, the paediatric indication covers children from 1 year (5 MS), 6 months (9 MS), or without restrictions (2 MS).
- *Haemophilus influenzae / membrane fraction of klebsiella pneumoniae / ribosomal fractions of klebsiella pneumoniae / streptococcus pneumoniae / streptococcus pyogenes* including:

  Ribomunyl (and associated name Immucytal), which was authorised as tablets in seven MS and as granules for oral solution in eight MS, for the prophylaxis of recurrent infections of the upper respiratory in children above 2 or 6 years old depending on the presentation and prevention of the recurrent surinfections in chronic bronchitis in adults.
- *Escherichia Coli/ Klebsiella Pneumoniae / Staphylococcus Aureus / Staphylococcus Epidermidis / Streptococcus Salivarius / Streptococcus Pneumoniae/ Streptococcus Pyogenes / Haemophilus Influenzae / Corynebacterium Pseudodiphtheriticum / Moraxella Catarrhalis* including:

  Polyvaccinum, which contains heat inactivated whole bacteria and is authorised in one MS as nasal drops for prophylactic and therapeutic treatment RURTI in adults and children from 6 months old and as suspension for injection for prophylactic and therapeutic use or adjunctive treatment in case of long-lasting, chronic and recurrent RTI in adults and children from 2 years of age.

Recurrent RTI of the upper airway (otitis media, mastoiditis, pharyngo-tonsillitis, adenoiditis and rhinosinusitis) (RURTI), represent the majority (80−90%) of such RTIs. Recurrent infections of the lower airway (RLRTI) (bronchitis/ bronchiolitis, tracheitis, pneumonia and exacerbations of chronic lung disease) are not easily managed since they are more severe and difficult to treat. A universally agreed definition of RRTI is currently lacking. Six or more URTI, or at least one infection per month during autumn and winter, in children >3 years of age, or eight or more episodes per year in children < 3 years old, have been proposed as suitable definitions (for patients without immunological deficiency, or functional/ anatomical alterations or other underlying pathological condition). A more generalised concept of RRTI is when a child displays a higher frequency of infections compared to peers from the

same age cohort and environment. Frequency of infections diminishes with growth, yet the average rate of infection in adults remains twice a year.

As mentioned above this review was initiated by the Italian National Competent Authority (AIFA) further to the results of recent studies becoming available considered to raise some issues related to the efficacy of these products in respiratory infections. Taking into account the known very rare risk of serious immunological reactions associated to these products, AIFA considered it in the interest of the Union to review the impact of these concerns on the benefit-risk of the class of bacterial lysates-based products in their authorised indications for respiratory infections.

In its assessment, the CHMP considered the totality of the data submitted from different sources. A summary of the most relevant data is included below. Based on sales data, the patient exposure is estimated at around 70 million patients over the past 22 years.

2.2. Data on efficacy

The MAH submitted the available data to support the efficacy of their products in their authorised indications and data on possible therapeutic failure or disease exacerbation. It was not possible to draw conclusion on possible therapeutic failure or disease exacerbation as data was limited or absent.

2.2.1. Luivac

The MAH submitted the results from five double-blind, randomised, controlled clinical trials (RCTs) encompassing a total of 859 patients treated with Luivac PIROL (Fischer 1990, FK-03/88, PAIS (Riedl-Seifert 1991, FK-08/90), LUISUISSE (Rutishauser 1996, FK-04/93), PASPORT (Ruah 1996, FK-09/92)) and ACASP (completed during this procedure) evidence for the therapeutic efficacy of Luivac as prophylaxis for RTI. Four of these trials (*PIROL, PAIS, LUISUISSE and ACASP*, encompassing 705 patients treated with Luivac) were placebo-controlled. Of the 705 patients treated in these three trials, 216 were younger than 12 years of age, at least 71 patients were ≤ 6 years old, and at least 361 patients ≥ 18 years old. The primary endpoint was a composite endpoint integrating heterogeneous symptoms related to the severity and duration of infections “severity of clinical symptoms” (SSC) in the first four RCTs and the number of episodes for the ACASP study.

In the *PIROL* study (Fischer, 1990) analysis was performed on 150 adult patients (between 18 and 50 years of age) who had received Luivac and on 153 patients who had received a placebo. Four full recurrences of infections of the respiratory tract per year (rhinitis, sinusitis, otitis, pharyngitis, laryngitis, bronchitis and mixed forms) were regarded as inclusion criteria. A statistically significant difference was observed between the two groups from week 12 ($p=0.0093$) until the end of the study in week 24 ($p=0.011$) with regard to the SSC score. Additional treatment of RTI was considered necessary for 89 patients receiving Luivac, and for 102 patients receiving placebo ($p=0.047$). Other secondary objectives such as number of infections, treatment with antibiotics (number, mean duration), days with absence from work, fever score and overall assessment by physicians were not significantly different.

The second placebo-controlled, double blind RCT (*PAIS* trial, (Riedl-Seifert 1991)) performed in 233 children aged 4-9 years included 99 children on Luivac and 108 on placebo in the efficacy analysis. Dosing was performed according to the posology. A significant difference in SSC score ($p=0.025$) was noted between Luivac (score of 2.6) and placebo (score of 4.7) after evaluation of the second treatment period. The total number of infections during this second period, recorded on the basis of relevant clinical symptoms, was also significantly different ($p=0.026$) with a reduction to half compared to the placebo group (15 Luivac versus 29 placebo). It is noted that the intervention is not well

described in the study report and that the study was conducted from February to July 1991, thus partly outside the season for RTIs.

The third double-blind placebo-controlled RCT (*LUISUISSE*, (Rutishauser 1996)) randomised children (aged 4 years and above) and adults (up to 65 years of age), with a high number of infections per year to active treatment and or placebo 2:1. In group A, 117 children (4-11 years old) received Luivac and 72 placebo, while in group B, 128 adolescents (≥12 years) and adults received Luivac and 83 placebo. Information provided regarding patients characteristic was insufficient to assess whether study groups were homogenous and balanced with regards to potential confounding factors. Patients who did not complete the entire treatment were excluded from the intent to treat (ITT) population. A statistically significant reduction was seen during the second treatment period in the SSC for both group A (reduction from 7.57 to 2.56 in the Luivac group versus 8.56 to 4.82 in the placebo group, p=0.038) and group B (7.16 to 2.20 versus 9.28 to 4.86, p=0.0046). The number of infections was also significantly reduced under Luivac treatment compared with placebo in both group A (p=0.016, rate of infections per patient 0.36 versus 0.58) and group B (p=0.032, rate of infections per patient 0.22 versus 0.39), as was the duration of infections (group A: p=0.0255, 1.74 versus 3.28 days, and group B: p=0.0038, 1.5 versus 3.33 days). Severity of infections was significantly reduced for group B only (p=0.005). The efficacy of Luivac was similar overall in children and adults compared with placebo-treated groups.

The fourth double-blind, RCT (PASPORT study; Ruah, 1996), compared two different treatment schedules, both with Luivac. One group received the currently authorised treatment schedule of two cycles, followed by two placebo cycles, whilst the second group received four treatment cycles. The results of the study showed that additional booster cycles following the first two treatment cycles did not result in any further benefit.

In the fifth RCT (ACASP, “Adult Clinical Assessment Study on Paspat”) adult patients were randomised to treatment or placebo for 12 weeks and were followed for another 6 months. The vast majority of observed infections occurred in the upper respiratory tract (163 versus 16), such that the inclusion of LRTI has no major impact on the outcome of the trial. Similar numbers of infectious episodes during the 6 months evaluation period were observed in both groups: 1.03 ± 1.39 episodes were observed in the Luivac group, 1.01 ± 1.21 in the placebo group. It was noted that the background infection rate was very low, and much lower than expected. It is also noted that the study had no prospective run-in period.

Additional evidence is available from several uncontrolled, open or retrospective studies enrolling over 10,000 patients (other studies). The patient population in these trials was similar to that in the RCTs described above and to the population Luivac is intended for, i.e. individuals with an increased rate of RTI. These studies reported a therapeutic benefit of Luivac in terms of reduced infection rate/severity after treatment and a variety of additional endpoints. However, this group of studies performed mostly descriptive evaluations, was not blinded and not placebo-controlled and presented a minimal amount of statistical evaluations.

Discussion

Luivac is authorised for the prophylaxis of RRTI in adults and children from 4 years of age. In one MS, the paediatric indication is restricted to RURTI. It is noted that children from 4 years of age onwards and adults up to 80 years have been included in the studies. The results of the studies have not been stratified according to age categories.

Four double-blind controlled randomized clinical trials compared Luivac with placebo in children, adolescents and adults as a prophylactic treatment in RRTI. Three studies demonstrated formally

superiority of treatment over placebo with regard to the primary endpoint which was a severity score of clinical symptoms of RTIs with unclear clinical relevance. Further, it remains unclear whether the score used was validated. Of note, secondary endpoints such as number of infections in the study period, treatment with antibiotics (number, mean duration) were not significantly different from placebo in study PIROL. In addition other shortcomings of the study design and conduct have been noted: interventions were not well defined in the study report PAIS and patients who did not complete the entire study were excluded from the ITT analysis in study LUISUISSE. No stratification of patients according to different underlying disorders is possible. Although patient characteristics are not described in detail, patients with serious chronic diseases of the respiratory tract or those treated with systemic corticosteroids for respiratory tract diseases previously were excluded from the studies. Thus, the studies' results are most likely related to URTIs (which are considered more frequent than LRTI in the study populations).

The fourth RCT was finalized during the referral procedure (ACASP). The primary endpoint was the rate of RTIs during the study period. However, this study failed to demonstrate superiority of the product compared to placebo in adults. Considering the low rate of RTIs in the placebo group, any effect from the products would have been difficult to observe in this study, thus these results should be interpreted with caution.

The evidence generated from the uncontrolled, open or retrospective is low. The studies included uncontrolled, non-interventional post-marketing surveillance studies and some of them compared number of infections after treatment with Luivac compared to documented infections in a previous reference period.

The authors of a review article on immunomodulators for the prevention of RTI in children (Cardinale, 2015) concluded that insufficient evidence of efficacy of Luivac was available in paediatrics.

It is noted that no patients with a history of chronic obstructive pulmonary disease (COPD), asthma and pneumonia/ bronchopneumonia appear to have been included in the clinical trials.

The data presented may suggest efficacy in children and more questionably in adults for the prevention of recurrent RTIs, mainly URTIs. Repeated dosing has not demonstrated additional effects.

2.2.2. Respivax

The MAH submitted the results from *in vitro* and *in vivo* studies as well as from 10 clinical studies in respiratory conditions, including two published placebo controlled studies. One of these two studies investigated the immune response of Respivax in 56 children and 30 adults and showed that Respivax can induce interferons (Kodjouharova, 1999). Whilst the second one in 50 children with recurrent acute bronchopneumonia showed favourable effects of Respivax with significant reduction of total number of inflammatory episodes, days with antibiotic treatment, days of stay in hospital and increase of the secretory IgA in saliva compared to placebo (Jossifov, 1989). A study evaluating the effects of Respivax on the immune system in patients with HIV was also submitted.

Table 1. Overview of studies conducted with Respivax

Study first author, year	Design and patient No. (Investigational product / control)	Results	Clinical significance of the results
Kisyova (year	Levamisol (n=63), IgA	Respivax treated pts: anti-	No statistics

Study first author, year	Design and patient No. (Investigational product / control)	Results	Clinical significance of the results
not stated)	gammaglobulin (n=17), Dipyridamole (n=91), Respivax (n=62) No double blind, no randomisation, no patient selection criteria. 5 year study	recurrent effect in 66.2%., treatment duration shortened in 82.25%; reduction of Phagocytic index + IgA influenced	% anti-recurrence effect (no definition), shortened treatment
Kisyova, 1989	Oral vs. inhalative Respivax 64 adults. No double blind, no randomisation, no patient selection criteria. 4 months study (some patients were followed up for 3 years)	Anti-recurrent effect in 82.2% treated pts., Reduction of no. and severity of inflammatory episodes vs. Control; increase of antibacterial ab titers	No statistics; immunological effects
Dobrev (year not stated)	Respivax in pats. 34 adults With COPD over 1987-1988 no patient selection criteria	Decreased number and duration of exacerbations of chronic bronchitis; Bronchial obstruction influenced; IgA+ other immune parameters stimulated	Changes from baseline, no statistics
Petrovska (year not stated)	Respivax in 20 adults with infectious-allergic bronchial asthma basic patient selection criteria. 240 days study.	Improvement of clinical and functional parameters for bronchial asthma	Changes from baseline, no statistics
Josifov, 1987	Respivax for prevention in bronchopulmonary infection in 50 children 4-12 years with at least 3	Significant reduction of total number of inflammatory episodes, days with antibiotic treatment, days of stay in hospital and increase of the	Changes from baseline; immunological

Study first author, year	Design and patient No. (Investigational product/ control)	Results	Clinical significance of the results
	bronchopulmonary infections, bronchitis and/or pneumonia in the previous year. 3 months study.	secretory IgA in saliva compared to previous year.	parameters; no statistics
Iliev (year not stated)	Immunological effect of Respivax 37 children 3-7 years screened with immunological tests and divided in 3 groups: non-specific pulmonary condition/pulmonary tuberculosis (n=10)/healthy group as control (n=10). 3 months study	Increased immunological parameters in treated children Reduction in no. and severity of respiratory episodes	Immunological parameters
Vasileva, 1990	Immunprophylaxis and Therapy158 children 10 mo-3 years with frequent ENT infections. 4 months study	80% of the children with a very good clinical effect	Abstract
Klinkanova, 1990	Infectious asthma 56 children aged 3-14 years	83% of the children with a very good clinical effect	Abstract
Kojuharova,	children 5-11 old with bronchial asthma (randomized to Respivax (n=35) or placebo (n=21)) and 20 adult patients with chronic nonspecific pulmonary diseases (Respivax (n=20)). 20 days study	Four-fold increase of interferon in 86% of Respivax patients 3 days post treatment	No efficacy investigated
Kojuharova, 1999	Impact of Respivax on Td-immune response in patients with chronic nonspecific	Significantly higher percentage of revaccinated individuals with high concentration of antitoxic	No efficacy investigated

Study first author, year	Design and patient No. (Investigational product / control)	Results	Clinical significance of the results
	pulmonary diseases aged 12-30 years old randomized to respivax (n= 47) or placebo (n=40). 20 days study	antibodies (78,7 ± 11,7%)	
Petrunov, 1996	Evaluation of respivax immunostimulation in 141 adults patients with HIV Basic patient selection. 3 months study	Stimulatory effect on different effector cells of host defense reactions	Interim results, immune parameters

Discussion

Respivax is indicated for immunotherapy and immunoprophylaxis of diseases of the upper and lower respiratory system in adults and children from 3 years of age suffering from recurrent and chronic infections of the respiratory tract. The indication lists a number of conditions including infectious bronchial asthma and infections of the respiratory tract which are resistant to antibiotic therapy.

The previous assumption of efficacy in the various infectious diseases of the respiratory tract is mainly based on studies investigating immunological parameters in subjects treated with Respivax. It remains unknown whether these immunological effects can be translated into relevant clinical efficacy.

No double-blind, randomised, placebo controlled, clinical trial investigating efficacy in the target group was performed. While the studies submitted show some positive effects, these suffer from major methodological limitations such as unclear selection of patients, unclear case definitions, lack of clinical relevant endpoints, observational character, limited sample size and lack of an adequate control group. Therefore, the submitted data do not allow definitely establishing the efficacy of Respivax its authorised indication.

2.2.3. Lantigen B

The MAH submitted the results from a meta-analysis (Melioli, 2016), as well as summary information from 12 studies in adults and 12 in children (please see below table). Of note, no publication or study report was available for most of these studies. The most frequent age categories included in these studies were from 1 year to 12 years and from 18 to 65 years.

Table 2. Overview of studies conducted with Lantigen B

Study first author, year	Design and patient No. (Investigational product/ control)	Condition	Primary endpoint	Follow-up (mo)	Results
Studies in prophylaxis of RTIs in adults					
Leigh, 1963	125 healthy persons 20-60 years of age	RTI	Days absence from work	6	85/114 finished study "spent a much better winter with diminution of symptoms and reduction of absenteeism"
Rollet, 1965	24 healthy persons Lantigen B No information on age of participants	Rhino-pharyngeal diseases	Days of absence from work	7.5	reduction of the number of days of absence : 62 days vs, 168 in control group
Phlean, 1966	157 healthy persons Lantigen B/Placebo (62/69) 30-50 y of age	At risk of RRTI		No informatio n	measurable benefit in 58% of Lantigen group versus 17.4% in placebo group
Newbold , 1971	52 patients Lantigen B/Placebo 25/27 17-30 y of age	RRTI		7	Days off/patients as reported in questionnaires: Lantigen B 0.76 vs. placebo 2.48,
Tyrrell, 1972	112 patients 18-68 oy f age	Common cold	No. of common cold episodes	3-6	oral vaccination for prophylaxis of colds is not a useful procedure
Meichen, 1976	2888 persons Lantigen B/Placebo (1446/1442) No information on age	Respiratory illness	days of absence from work	6	Respiratory illness during the winter: 26.7 % of Lantigen B group vs 30.6% in placebo group

Study first author, year	Design and patient No. (Investigational product/ control)	Condition	Primary endpoint	Follow-up (mo)	Results
Meichen, 1981	Double-blind RCT 2888 healthy volunteers Lantigen B/Placebo 1262/1255 analysed (1446/1442 included) Age: 15-55	Influenza, bronchitis and cold Patient characteristics not provided	No. of days of absence from work, Sickness time as surrogate for RTI Selected on the basis of personal records	7	Combined incidence: 26.7% vs 30.6%, p<0.05; concomitant treatment not provided
Cerreta, 1983	20 patients Lantigen B/Placebo 10/10 No information on age	RRTI	No information	1	Lantigen B significant better than placebo
Peona, 1984	20 pts. Lantigen B/ Placebo 15/5 No information on age	RRTI	Clinical symptoms	No information	All treated patients experienced very good or good results
Pozzi, 2004	Double-blind RCT: 118 patients Lantigen B/Placebo 56/62 Mean age 72 (50-94)	RRTI	Reduction of the number of infectious episodes	6	Mean incidence of recurrence 0.73 placebo vs. 0.56 Lantigen B group; NS. Secondary endpoints, e.g. fever and cough had a similar, non-significant trend

Study first author, year	Design and patient No. (Investigational product/ control)	Condition	Primary endpoint	Follow-up (mo)	Results
Braido, 2014	Multicentre RCT, 160 patients, Lantigen B/Placebo 79/81 (58/59 analysed), Mean age 42	RRTI: URTI + LRTI ≥ 2 URTI in previous year	reduction of the number of infectious episodes (IE)	8 mos + 6 mo FU	Infectious episodes in 8 months ANCOVA analysis, adjusted for baseline covariates: Placebo 1.43 (CI 1.01-1.86); Lantigen B group 0.86 (CI 0.54-1.19), p=0.036
De Bernardi, 1992	60 patients Lantigen B/ Placebo 40/20	RRTI chronic bronchitis COPD	frequency and intensity of exacerbations	4 months	Exacerbations: 1.7 Lantigen B group vs 4.1 placebo group
Carta, 1994	30 patients Lantigen B/Placebo 20/10 45-72 years of age	RRTI COPD	Reduction of the number infectious episodes	2 months	Mean no. IE: 1.8 Lantigen B group vs 5.3 placebo group
Studies in prophylaxis of RTIs in children					
Price, 1974	196 volunteers Lantigen B/Placebo 97/99 (following 45 withdrawals) Age: 10-17 years	URTI (Sneezing, dry throat, running nose and sneezing sore throat)	Absence from school activity	6	No. of days absent: 15% vs. 32% in favour of Lantigen B (p<0.005). Average No. of colds per person not different. 37.2 % of diaries not returned, centre effect

Study first author, year	Design and patient No. (Investigational product/ control)	Condition	Primary endpoint	Follow-up (mo)	Results
Price, 1976	110 volunteers Lantigen B/Placebo (merthiolate) 55/55 Age: 7-13years 22 girls participated in study in previous year	URTI	No of colds, absenteeism	6 months FU (Results in the second year)	No. of days of absenteeism in the treatment group significant lower compared to placebo. No good matching of results obtained by teachers, doctor, matron
Nespoli, 1987	18 patients Median age 4.6 years	RRTI	Efficacy compared with previous year	6	In 14 pts. (78%) efficacy was judged as excellent or good
Galli, 1987	33 children 2-14 years of age every child was its own control	RRTI	Reduction of no. of absence from school 2 years of the scholastic history	6	Days of absence from school: 11 Lantigen B group vs 21 placebo group
Magnolfi, 1987	20 patients Lantigen B/Placebo 10/10 3-7 years of age	RRTI	IE	6	Nb of acute infections reduced by Lantigen B (-22%)
Rossi, 1994	30 patients Lantigen B/Placebo 15/15 3-7 years of age	Frequent RTI	IE, days of disease, days with fever antibiotic therapy	1	reduction of the number of days with fever (0.6 vs 2.9) in favour of treatment group

Study first author, year	Design and patient No. (Investigational product/ control)	Condition	Primary endpoint	Follow-up (mo)	Results
Rossi, 1994	40 patients Lantigen B/Placebo 20/20 1-5 years of age	RRTI	evaluation of the frequency of infection during the follow-up period	3	Infections/month: 0.57 in the treated group vs 1.28 in the placebo group
Sorge, 1994	40 patients Lantigen B/Placebo 20/20 1-13 years of age	RRTI	reduction of the number of infectious episodes, of the days with fever and antibiotic use	4	Days with fever: 1.75 in the treated group vs 3.45 in the placebo group
Castello, 1996	30 patients Lantigen B/Placebo 15/15 2-12 years of age	RTI	Immunological parameters	3	Increase in IgAs. The differences in the number of infectious episodes were not significant
Moratti, 1999	52 patients Immubron/Lantigen B/Placebo: 20/7/26 3-12 years of age	post-surgery immunodeficiency in ENT paediatric patients.	number of infectious episodes during the 6-month follow up was recorded	6	No. of infectious episodes in FU: Immubron/Lantigen B/Placebo: 25 (20 patients) 6 (7 patients) 127 (26 patients)
Pozzi, 2004	Double-blind RCT, Lantigen B (n=47)/Placebo (n=47) 11 drop outs Mean age 3.4 (1,5 to 15,2 years)	Recurrent respiratory infection, Patient selection unclear	reduction IE	6	Mean incidence of RTI 1.64 in placebo group and 1.21 in Lantigen B group, NS. Similar, non-significant trend in secondary endpoints

Study first author, year	Design and patient No. (Investigational product/ control)	Condition	Primary endpoint	Follow-up (mo)	Results
Chen, 2005	86 patients Lantigen B/Placebo 43/43 2-12 years of age	RTI		8	significant reduction in the frequency of RTI, number of days with fever and number of days of using antibiotic

The meta-analysis submitted included data from 7136 patients from 23 randomized clinical trials conducted between 1963 and 2014, all reflected above, were included (Melioli, 2016). The analysis found that Lantigen B induced a significant reduction of infections vs placebo: the relative risk (RR) was -0.42; 95% CI = -0.33 and -0.47. The RR was always in favour of Lantigen B in all the other subsets analysed, in particular in adults with RTI (RR = -0.50; 95% CI =- 0.35 and -0.65) and in children (RR = -0.50; 95% CI =- 0.23 and -0,78).

Discussion

Lantigen B is indicated depending on MSs either for prophylactic and therapeutic treatment of RURTI or bacterial URTI in adults and children, as prophylaxis of RRTI in adults and URTIs in children or for the prevention of RRTI in adults and children from 3 years of age.

Considering the small sample size of the majority of studies evaluating the efficacy of Lantigen B in the prophylaxis of RTI and the lack of classification in subgroups of recurrent respiratory diseases it was not possible to analyse different conditions of RTIs, nor the effect according to age. Many of the studies had further methodological limitations. In particular studies performed up to the nineties were carried out without a formal definition of all relevant parameters to be considered. It should also be noted that publications or study report werenot available for a majority of the studies, thus precluding a thorough assessment.

The more recent studies in the prophylaxis of RTI in adults show conflicting results. Indeed, in the study by Pozzi and colleagues (2004) no superiority over placebo was demonstrated. In contrast the results of the double blind, placebo controlled, multicentre clinical trial published by Braido and colleagues (2014), showed statistical superiority of infectious episodes of the treatment group versus placebo (placebo group a mean of 1.43 (C.I. 1.01–1.86) episodes in the 8 month study period, while 0.86 (C.I. 0.54–1.19) episodes were recorded in the treatment group). However, the results of this study should be interpreted with caution for the following reasons:

- The primary outcome did not allow any discrimination between upper and lower RTIs and it is likely that the results observed are driven by the more frequent URTIs.

- A relevant placebo-effect has been observed and a similar trend of infections reductions has been reported between groups.

- Drop-outs (40/160 (25%) patients) were not included in the analysis.

- The primary analysis model used a t-test (for normally distributed, continuous data) however, the number of infections are better described as count data (e.g. by a negative binomial distribution).

Especially as about 40-50% of patients had no infection, the assumption of normality may not be appropriate. At baseline, an imbalance in the frequency of infections in favour of Lantigen B was noted (mean: 3.78 placebo; 3.54 Lantigen; p = 0.023).

A number of limitations should also be noted with regards to the meta-analysis conducted by Melioli and colleagues which reported favourable effect of Lantigen B in the prophylaxis of RTIs. As mentioned above, number of the RCT included had small sample sizes, inadequate study designs, and were heterogeneous in term of endpoints analysed, age groups, conditions (prevention of RRTI, RRTI), and study designs. The adequacy of the chosen combined efficacy measure (reduction of number of exacerbation, days of illness for RRTI, number of days with fever, number of days of absence from work or from school) is questionable as the parameters selected are not completely comparable. A systematic assessment of the risk of bias in the RCTs included as it is obligatory for systematic reviews and was not provided by the authors although they sporadically addressed sources of bias for each RCT. Against this background, the question arises whether the obtained result for the main combined efficacy measure, a reduction of -42% of the main outcome parameters of the various studies (95% CI -0.35; -0.47) with the measures of heterogeneity clearly supporting the very large inhomogeneity (Q=437.0, I2=94.7) can be reliable. The MAH plans to revise this meta-analysis.

Altogether, a number of old studies of low quality suggest some limited benefit in the prophylaxis of RTI in children. In contrast, the most recent study with a more robust design failed to show a statistically significant improvement (Pozzi, 2004). Conflicting results are also observed in the prophylaxis of RTIs in adults, based on the studies with a more robust design.

Whilst patients with undifferentiated RTI were included in most studies, two studies including a total of 60 patients specifically evaluated the effect of Lantigen B in LRTI. Whilst these studies reported a positive effect of Lantigen B, several methodological limitations have been identified, such as very small sample sizes, lack of clear age stratification, low quality evaluation of endpoints, inadequate control group and lack of disease definition. Moreover, overestimation of treatment results cannot be excluded since all possible confounders have not been taken into account in the analysis. Therefore these studies do not allow definitely establishing the efficacy of this product.

No studies were conducted to evaluate a curative effect of Lantigen B. The MAH clarified that clinical data focus on the prophylaxis of RTI and that the “treatment” term was intended to indicate Lantigen B as a “therapeutic agent” in patients with recurrent RTI but never as therapy of acute events. Consequently, the MAH proposed to remove this indication.

In addition, the MAH clarified that Pneumonia was never specifically indicated as one of the diseases that can be prophylactically treated with Lantigen B.

2.2.4. Buccalin

The MAH submitted the results from a RCT in adults (Carlone, 2014 - *BUC-SI-11-001*), a retrospective observational trial in elderly with COPD (*BUC-SI-11-002*) and a published retrospective study on paediatric patients (Ramponi, 2015).

Study *BUC-SI-11-001* was a double-blind, placebo-controlled, randomised, multicentre trial investigating both upper and lower RTI in adults (18 to 65 years of age). The participants had a history of previous infectious episodes of the respiratory tract (2-6 RTI in the previous year). The primary endpoint was the number of days with respiratory infections in a 6-months follow-up period. During the 6 months of follow-up the mean number of days with infectious disease was significantly larger (p = 0.032) in the placebo (7.5 ± 10.6) than in the Buccalin group (6.6 ± 8.0). No between-group difference was observed in the severity of the infectious episodes, evaluated after 4 and 6 months. The

severity of different signs and symptoms related to the infectious episodes, such as fever, pain, dyspnoea and cough as monitored by subject's diary and CRF, did not differ between placebo and Buccalin. The disease free period, evaluated as the time of occurrence of the first infectious episode after the end of the treatment cycles, was longer in the active group [138.0 (95% confidence interval: 126.5, 149.5) days] than in the placebo group [128.1 (113.7, 142.5) days], however, the difference was not statistically significant (Log rank test p = 0.302). The number of days lost at work or school was neither significantly different between the two treatment groups for the first 4 months (placebo: 0.9±2.4 days vs. Buccalin: 1.3±3.5 days, p=0.317) nor for the whole observation period (1.0±2.5 vs. 1.3±3.5 days, p=0.461). The global efficacy, evaluated by the Investigator documented a similar rate of improvement in the two study groups. The general well-being, evaluated by the subjects showed no significant differences after 4 treatment cycles, between the placebo and active treatment group (7.5±1.5 vs. 7.2±1.6, p=0.321). Similar results were observed after 6 treatment cycles (7.8±1.3 vs. 7.7±1.4, p=0.724). Treatment with antibiotics, anti-inflammatory drugs and bronchodilators was not significantly different between the two groups.

Study *BUC-SI-11-002* was a retrospective, chart-based study of the frequency of RTI in GOLD II-IV stage COPD patients in the treatment year (2009 or 2010) compared to the previous year. The main efficacy endpoint was the reduction of at least one episode during the year of treatment compared to the previous (control) year. The analysis of the charts of all patients (n=68) aged 44-88 (mean 71) showed a reduction in the number of respiratory infections (-53% vs control), the overall number of days of illness (-71% vs control), the number of hospitalisations for severe exacerbations (figure not specified), the severity of exacerbations (figure not specified).

The retrospective study on paediatric patients with a history for recurrent respiratory infections (≥3/year) who received at least a cycle of Buccalin in the period 2008-2013, recorded and analysed the frequency of episodes in the treatment year, compared to the previous one (Ramponi, 2015). The study involved a total of 70 patients (mean age 9.2 years, range 4-16) treated with 1-3 monthly cycles and reported a significant reduction (67%) in the number of infectious episodes.

In addition, the MAH submitted a number of older published studies in adults and children, as well as pre-clinical studies. Out of these published studies, 3 were RCTs and are summarised in the below table. It is unknown whether the findings from pre-clinical studies can be translated into a clinical effect.

Table 3. Overview of older RCTs conducted with Buccalin

Study first Author, year	Patient No. (Investigational product/ control)	Condition(s)	Administration and dosing schedule	Primary endpoint	Duration	Result(s)
Guerra, 1992	90 patients history of bronchopneumonia or RRTIs Ig+Buccalin/Buccalin/no treatment 30/30/30 50-75 years old	URTI, pneumonia, bronchitis	1 tablet. on day 1, day 2, day 3 each, procedure was repeated after 3 months	Frequency of RRTI and most relevant immunological parameters	FU: 1 year	Reduction of RRTI

Study first Author, year	Patient No. (Investigational product/ control)	Condition(s)	Administration and dosing schedule	Primary endpoint	Duration	Result(s)
Stadler, 1997	80 healthy adults Buccalin 5 days/Buccalin 3 +placebo 2 days /Buccalin 5 days 10 fold concentr. /placebo 20/20/20/20 18-62 years old	immunisation	Oral, Standard dose or 10 fold dose cycle was repeated after a 60 days interval	Safety and immunogenicity of three different vaccination regimes	04/1997 to 10/1997	In the preliminary study report provided specific immune response against bacteria included in vaccine and an unspecific stimulation of the immune system. No statistical analysis was povided
Zanasi, 1992	26 subjects Buccalin/controls 11/11 Age; 49-77 years	chronic bronchitis (COPD?)	3 treatment courses	immunomodulating action of oral Buccalin	90 days	Increase in phagocytic activity in polymorphonuclear neutrophils vs. control

Discussion

Buccalin is indicated for the prophylaxis of RRTI in adults and of bacterial RURTI in children older than 6 months or for the prophylaxis of bacterial RTI without age limits.

In the RCT in adults (study *BUC-SI-11-001*) Buccalin was statistically significantly superior to the placebo for the primary endpoint i.e. mean number of days with respiratory infections. However the clinical relevance of the small difference observed between the two groups is questionable (6.6 ± 8.0 vs 7.5 ± 10.6), further it was not associated with a significant effect on clinical relevant secondary endpoints. For example no difference has been observed on the use of concomitant therapies and on days of absence from school or work, or severity of symptoms. This study included patients with 2-6 RTIs in the previous year, thus healthy patients may have been included.

The retrospective studies conducted more recently in a limited number of adult patients with COPD and children with RRTI as well as the earlier studies do not provide robust evidence of a clinical effect of Buccalin in the prophylaxis of upper and lower RTI due to serious limitations of the study design such

as small sample size, retrospective design, lack of randomisation, of blind, and heterogeneity of enrolled populations.

In vivo and *in vitro* data aiming to demonstrate the immune stimulatory effect of the medicinal product have not provided a validated surrogate parameter for efficacy. Thus, it remains unclear how these results translate into clinical efficacy.

2.2.5. Ismigen

The MAH submitted the results from 15 clinical studies in adults (including 4 RCTs), adolescents and children (including 3 RCT), 3 observational studies in children and a meta-analysis, all investigating the efficacy of Ismigen in the prophylaxis of RTI. No studies evaluating the efficacy of Ismigen in the treatment of RTI were provided.

Clinical trials in the prophylaxis of RTI in adults

A double blind placebo controlled RCT investigated the efficacy of Ismigen in the prophylaxis of URTI in 47 adults (25-80 years of age) (Tricarico, 2004). The primary endpoint was the number of infections. During the treatment phase and 3 months follow-up period, the number of respiratory infections (and their duration) was significantly lower in the group treated with Ismigen sublingual tablet compared to patients who received placebo (during 3-months treatment 7 vs. 31 respiratory infections, during 3 months follow up 3 vs. 16, $p<0.01$).

Three further open studies investigated efficacy in the prophylaxis of URTI in adults. In the first of these open controlled studies, 114 patients were divided equally in three groups receiving respectively Ismigen, a bacterial lysate comparator or no treatment (Macchi, 2005). During the treatment period, the mean number of URTI in the Ismigen group was significantly lower (Mean number of URTI/patient: 0.34) as compared to both the comparator group (mean number of URTI/patient: 1.0) and the control group (mean number of URTI/patient: 1.23); $p<0.05$. During the 3 months of treatment, Ismigen was significantly better in reducing the duration of URTI (mean duration/patient: 2.46 days) either as compared to the comparator (mean duration/patient: 4.72 days), or to the control group (mean duration/ patient: 5.17 days) $p<0.05$. The same results were also observed during the 3 months follow-up period. In the Ismigen group the number of lost working days were significantly fewer (mean number of working days lost: 0.15 days/patient), as compared to both comparator (mean number of working days lost: 2.80 days/patient), and control group (mean number of working days lost: 5.40 days/patient), $p<0.05$). In addition over the complete study period, significantly less patients (0) required antibiotic treatment compared to the control group (9), $p=0.002$. In the second open study, which was uncontrolled, treatment with Ismigen increased secretion of salivary Immunoglobulins in 40 patients with recurrent URTI (Braido, 2011). In the third study 23 patients given Ismigen required significantly less antibiotic treatment (0) than 46 patients treated with a bacterial lysates comparator (6) or not given bacterial lysates product (13).

Clinical trials in the prophylaxis of LRTIs adults

Three RCT investigated the efficacy of Ismigen in the prophylaxis of LRTI in adults.

Boris and colleagues (2003), carried out a controlled, single blind, RCT involving 300 patients (150 treated with Ismigen and 150 treated with a multivitamin preparation as a placebo) (average age 62.9 ± 5.67) with previously treated tuberculosis and with history of episodes of infective recurrences in winter season. Significantly fewer bronchial infections were reported in Ismigen group (85) than in the placebo group (232), ($p<0.05$). In addition, based on an illness severity score (ISS) visuoanalogical scale the severity of the infectious episodes in patients treated with Ismigen was lesser (-34%) than in the patients with placebo ($p<0.05$). The absolute number of days under antibiotic therapy was equal to

1,305 days in the group treated with placebo versus 645 days in the group treated with Ismigen. It is noted that the placebo was a multivitamin preparation and that there was only a very brief description of the methodology in the publication. Thus, it is unclear whether the blinding was ensured.

Cazzola and colleagues (2006) evaluated in a double blind placebo-controlled clinical trial the duration and severity of acute exacerbation of COPD (AECOPD) in 178 patients with moderate to very severe COPD. In the Ismigen group, the mean duration of acute exacerbations was significantly shorter, than in the placebo group (10.6 days vs. 15.8 days: 34% decrease), ($p<0.05$). In addition during the 12 months follow-up significantly fewer episodes of infectious exacerbation of COPD were reported in the Ismigen group (2.3 ±0.3 cases/patients/year) compared to the placebo group (2.9 ±0.4), $p< 0.05$. Clinical recovery related to respiratory symptoms was 89.3 % in the treatment and 81.8 % in the placebo group. It remains unclear if the statistical analysis accounted for the interim analysis conducted after 3-6 months. The placebo was not described in the publication.

The AIACE (Advanced Immunological Approach in COPD Exacerbation; Braido, 2015) study was a multicentre, double-blind, placebo controlled RCT in 288 patients aged 40 years old or more with moderate, severe and very severe COPD according to GOLD classification. No statistically significant improvement was observed for the primary endpoint (number of exacerbations/patient/year) as 0.51 were reported in the in the Ismigen group and 0.52 in the placebo group. Significant difference from placebo was observed for some secondary endpoints such as number of days of hospitalisation due to COPD exacerbation, but not for others such as use of antibiotics, NSAIDs, bronchodilators and mucolytics. An ancillary RCT evaluating the production of antibodies directed to respiratory and systemic pathogens in 23 patients reported a reduced number of seroconversion, of infectious episodes and COPD exacerbations (Ricci, 2014).

In addition, three small studies in COPD patients reported favourable effects of Ismigen on symptoms of dyspnoea (open study by Rossi, 2004), the number of exacerbations, need for oral corticosteroids or antibiotics (RCT by Cazolla, 2009) and the number of bronchial infections and antibiotic use (open observational study by Cogo, 2003).

Clinical trials in the prophylaxis of RTI in children

Three RCTs (one double blinded and two open studies) investigated the efficacy of Ismigen in the prophylaxis of RTI in the paediatric population. In addition, a further double-blind RCT investigated the efficacy of Ismigen in asthma control, in the paediatric population; results are presented as, whilst this is not an authorised indication for Ismigen, asthma exacerbations are often caused by respiratory infections.

The first placebo controlled RCT was performed in 180 children age between 5 and 10 years with a history of at least 4 episodes of RTI during the previous winter (Aksic, 2005). The study reported significantly fewer episode of infection in patients treated with Ismigen (169 infections) compared to those treated with a placebo (374 infections; -54%, $p< 0.01$). Of note the minimum criterion of severity for recording the infectious episode was specified *post-hoc* as that of having caused at least one day of absence from school.. Furthermore, the Ismigen group was divided into two sub-groups, one in which special care was given to the correct administration of the treatment (e.g. using motivating games or stories as relevant) and one in which no special measure was introduced. This may have introduced bias. No detailed study report and statistical analysis plan have been provided. The quality of the study and the results are questionable.

The second controlled RCT was open, and enrolled 120 children aged 4-9 years with recurrent rhinopharyngitis and/or otitis media and/or recurring pharyngo-tonsillitis (La Mantia, 2007). The study population was subdivided into three groups of 40 children. One group was treated with Ismigen, a

second was treated with a chemical lysate capsule (CL) and a third group received no treatment (control). Based on patients diary the average number of infectious episodes in the Ismigen group was significantly lower than that is the comparator or in the control groups. In addition, the average duration of infective episodes was 6 days in the control group, 5 days in the CL group and only 3 days in PMBL group. The authors did not describe randomisation and patient characteristics in the publication, thus the risk of potential bias cannot be assessed.

The third controlled RCT, also open, was performed in 85 children aged 10 months to 10 years with history of RRTI based on case history, most likely URTIs as children manifesting acute LRTI during the study were to be excluded (Rosaschino, 2004). Twenty-three (23) of the children were not given any treatment (control group). Patients younger than 48 months and those aged 48 to 60 months who were still immature were taught to use a simple handmade device facilitating the administration of the crushed tablet. The study reported a reduced mean number of recurrent respiratory infections with Ismigen (4.78) compared to the (6.78) untreated control ($p<0.05$) and compared to the same children for the previous year (4.78 vs 7.84, $p<0.05$).

The fourth placebo controlled, double-blind, RCT enrolled 152 patients (6-16 years of age) with allergic asthma (EOLIA study, Emeryk, 2018). No difference was observed between both groups for the primary end points (asthma control level). Significant improvements were reported for some secondary endpoints such as asthma exacerbation (1.1 ± 1.3 vs. 1.9 ± 2.0).

Three observational studies in a total of 162 children aged 3-15 years also reported favourable effect in the number of children with symptoms of recurrent infections, in the incidence of respiratory infections, in the frequency of tonsillitis and exacerbation of bronchial asthma.

Meta-analysis in RTI

A systematic review assessed a number of studies (some of those described above and two unpublished studies) investigating randomised comparisons of Ismigen with a placebo or no treatment (control) (Cazzola, 2012). The primary outcome measure was the prevention of exacerbations or acute RTI. The results were expressed as relative risk (RR) and the number of patients needed to treat for one to benefit (NNTB) calculated for 1 year to avoid one infection, the efficacy of Ismigen being determined with respect to the number of recurrences of RTIs. After combining the selected studies, the author concluded that Ismigen induced a significant reduction of the infection rate in patients treated with Ismigen (1.27 versus 2.01 for placebo), the absolute risk reduction being 0.87 and an NNTB of 1.15. According to the authors, results for sub-analyses of data were also provided for 7 RCTs in adults suffering from recurrent respiratory infections other than COPD, chronic bronchitis and tuberculosis reporting that Ismigen had a significantly positive impact on the reduction in the total number of infections. The authors also claimed that data from 3 RCTs investigating the effect of Ismigen in children (La Mantina, Roschino and Aksic) also showed a significant beneficial effect of this treatment.

Discussion

Ismigen is indicated for the prophylaxis of RRTI in adults and in some MS for the treatment of acute, subacute recurrent or chronic RTI as well as in one MS in children from 3 years of age.

The number of URTI were statistically significantly lower in the Ismigen group compared with placebo in a small double blind placebo controlled RCT in adults (Tricarico, 2004). These results are supported by additional studies in adults with less robust study design and quality. Limitation to these supportive studies include their open character of the studies, lack of control, unclear selection criteria of patients (history of infectious episodes) and small sample size.

Conflicting results were obtained from two double-blind placebo controlled RCT evaluating the efficacy of Ismigen in the prophylaxis of LRTI in adults (Cazzola 2006 and Braido 2015 [AIACE study]). It is questionable whether the results of the Cazzola study are clinically relevant (duration of acute exacerbations 10.6 days vs. 15.8 days and 2.3 ±0.3 vs. 2.9 ±0.4 episodes of infectious exacerbation of COPD/patients/year) and the appropriateness of the statistical analysis could not be fully ascertained. The AIACE study which is well-designed failed to demonstrate superiority over placebo for the primary endpoint (number of exacerbations/patient/year). Of note in this study, the background infection rate was very low, which complicates the interpretation of these results. Thus, there is no consistent evidence of efficacy in LRTI in adults treated with Ismigen. Further studies reported positive results however these had significant methodological issues (e.g. in the single-blind RCT study by Boris, there is uncertainty regarding the blinding) or the studies had small sample size and an open design.

In the paediatric population, the RCTs in the prophylaxis of RTI suffered from several methodological limitations and potential bias (e.g. specific motivation of the treatment group, hand-made application device, post-hoc changes of the study protocol, and uncertainties about selection and randomisation of participants). Further the double-blind, placebo-controlled, RCT in patient with asthma (non-authorised indication) failed to show superiority over placebo for asthma control (primary endpoint), while significantly fewer asthma exacerbations for the total study period were reported in the treatment group, the difference is of questionable clinical relevance (1.1 ± 1.3 vs. 1.9 ± 2.0). Positive results were observed in smaller, open studies. Stratification of the results with regard to different age groups was not provided.

The systematic review provided is not considered to provide robust evidence of efficacy. Limitations to the most of the studies included are described above. Further, the studies were not assessed for risk of potential bias and not grouped for double-blind or open clinical studies. Heterogeneity was noted for the 15 studies included (Q-Value: 42.133, I square=67 %).

The MAH clarified that any protective effect that Ismigen may bring regarding the development of pneumonia would be due to its effect on the prevention of URTI, but that it is not intended to substitute for pneumococcal vaccines or *Haemophilus influenzae* vaccine. The MAH proposed to include a warning in the SmPC in order to clarify this point.

No study evaluating the effect of Ismigen in the treatment of RTIs was identified. The MAH further clarified that the treatment indication was not based on a curative effect on the acute phase of the disease but rather meant to prevent subsequent complications related to the respiratory infections.

Limited data in adults and more limited data in children may support the efficacy in the prophylaxis of RTIs.

2.2.6. Broncho-vaxom

The MAH submitted the results from 15 double-blind, placebo controlled, randomised, parallel group trials conducted in adults and children with recurrent RTIs and/or exacerbations of COPD/CB. Out of these, 5 were considered non-conclusive by the MAH (BV-2007/02, BV-2007/04, BV-2007/06, EBV-09/01, BV-2005/01) and reported no difference in the primary and most secondary endpoints between the Broncho-vaxom and the control group. However the conduct of these studies suffered from GCP issues and therefore the results cannot be fully relied upon. In addition to these MAH-sponsored studies, the MAH presented the results of 25 published studies, meta-analysis or review articles.

Prophylaxis of RTI in adults

Study *BV-1991/11*, a double-blind, placebo-controlled, randomised study included 40 haemodialysis patients, aged 20-80 years, with a documented history of RTI (≥ 1 documented episode of RTI treated with antibiotics in the previous 12 months) (Tielemans, 1999). The primary endpoint was the number of RTIs in compliant patients (35 out of 40 patients); the number and duration of antibiotic treatment courses was also taken into account. The number of RTIs differed significantly (p=0.0176) in favour of Broncho-Vaxom during the last period of the study (weeks 13-24), no effect was seen in the two other periods (total 4 vs. 8 infections). However, the definition of RTI was modified *post hoc*. Further, there was a lack of type I error control and the analysis was restricted to the 'compliant' patients. Thus, the study is not considered to provide statistical proof of superiority over placebo.

Prophylaxis of LRTI Adults

In study *BVA-8701-FR-8801-5351* (1998) 396 patients age 65 years and older and who suffered from chronic bronchitis and mild COPD were randomised 1:1 in double-blind to receive a treatment with Broncho-Vaxom or a placebo (Derenne, 2003). 324 patients were included in the primary efficacy analysis. The primary endpoints were the number and the frequency of superinfections. No statistically significant difference was reported between the two treatment groups for both primary endpoints (superinfection free patients: p = 0.1, frequency of superinfections: p = 0.028). There was no type I error control for two of the endpoints and 72/396 patients were excluded from the primary analysis. Furthermore, heterogeneity of both groups was noted. The study protocol was amended during the conduct of the study resulting in to different subpopulations with differences in efficacy results.

Study *PARI-IS* (1995) was a double-blind, placebo-controlled, randomised study in 382 adults (mean age 66 years) suffering from severe COPD (Collet, 1998). No significant difference was reported for the primary endpoint as 44.5% and 43.7% of the patients experienced at least one AECB episode in the Broncho-Vaxom and placebo groups respectively (p = 0.872). Fewer patients were hospitalised in the Broncho-Vaxom group than in the placebo group (16.2 % vs. 23.2 %; p=0.089, ns), the average duration of hospitalisation was also shorter in the Broncho-Vaxom (1.5 days vs, 3.4 days; p= 0.037). There was no statistically significant difference in change in cough and sputum, quality of life but improvement of dyspnoea in Broncho-Vaxom group. The study was analysed based on an *ad hoc* interim analysis because of delayed start of study and low recruitment in the season, continuation in the next season was not recommended by experts.

Study *RCT BV-1996/7* was a double-blind, placebo-controlled trial performed in 276 patients with CB or COPD (GOLD stage I-II) aged 40-75 year old (Soler, 2007). The results revealed no overall significant difference between treatment groups regarding the monthly frequency of acute exacerbations (p=0.08) by the end of the study period at 6 months (primary endpoint). However a significant difference in favour of Broncho-Vaxom (mean AECB was 0.86 vs. 1.02; p = 0.03) was noted at the end of active treatment (at 5 months). Of note values for FEV1, FVC, FEV/FCV1 calculated from CRF and values FEV/FVC reported by investigators differ by an average of 16%, the former being frequently non pathological. The statistical analysis is questionable as count data were evaluated using methods for continuous normally distributed data. Thus, the study is not considered to provide statistical proof of superiority over placebo.

Prophylaxis of RTI children

Study *BV-1996/8* was a double-blind, placebo-controlled RCT in 232 children (3-8 years of age) suffering from URTIs at admission and from recurrent URTIs in the last 12 months (Schaad, 2002). Monthly frequency of URTIs was the primary endpoint. The result revealed a 15 % reduction of URTIs with Broncho-Vaxom compared to placebo. The cumulative mean reduction per subject was 0.4 URTIs.

The overall difference between both groups was borderline significant (p=0.05). Secondary endpoints such as intensity or duration of URTI, consumption of antibiotics, numbers of otitis, sinusitis and school absentees were not significantly different. The clinical relevance of the effect is questionable. Notably, the statistical analysis is questionable as count data were evaluated using methods for continuous normally distributed data. The algorithm for diagnosis of URTIs was re-defined during the study.

Study *OM85BVM01-97* was a double-blind, placebo-controlled RCT in 54 children (1-12 years of age) (Grief, 2013). The primary endpoint was the number of RTI during 12 months. The cumulated number of RTIs in the months 0-12 was significantly lower for active treatment ($p < 0.001$). A t-test was performed for the analysis whereas a non-negative binomial GLM model would be more appropriate.

Study *OM85BVM01-96A* was a double-blind, placebo-controlled RCT in 200 children (6-13 years of age) (Jara-Perez, 2004). The primary endpoint was also the number of RTI during 12 months. The number of RTI months 0-6 was significantly lower for active treatment ($p < 0.05$). A t-test was performed for the analysis whereas a non-negative binomial GLM model would be more appropriate. The selection of participants is not well described.

Study *BV-8502* was a double-blind placebo-controlled RCT in 127 children aged 6 months to 19 years and with ≥ 3 URTIs in the preceding 6 months (Paupe, 1991). The primary endpoint was the frequency of infectious episode and treatment index for severity. Overall there was a significant advantage for active treatment ($p< 0.05$) in each of the observed periods. A subgroup analysis by age revealed that the effect was based on children below the age of 6 years, whereas no significant effect was seen for those above 6 years of age. The population was very heterogeneous with regard to age but also concerning background diseases (n=14 subjects with cerebromotor impairment and/or trisomy 21 and hospitalisation). There was no correction for multiple testing.

Study CBVE-89-01 was a double-blind placebo-controlled RCT in 423 children of 6 months of age and older with risk for RTIs (Collet, 1994). At the end of the follow up period there was no significant difference between Broncho-Vaxom and placebo with regards to the number of RTI.

Published literature in the prophylaxis and treatment of RTI

Published articles reporting the results of studies in adults (11) and children (15), review articles in children (7) and meta-analysis (4) were submitted. Relevant ones are summarised in the below table.

Table 4. Overview of relevant Published articles conducted with Broncho-Vaxom (BV)

Study first Author, year	Condition	No of participants/ age	Study design	Result(s)
Studies in prophylaxis of RTI				
Koatz, 2016	Recurrent RTIs in allergic rhinitis, or asthma, or COPD	N= 84 16-65 years of age	open-label, prospective, sequential study	45% reduction of RTI with BV treatment ($p < 0.05$). Temporal effects not addressed

Study first Author, year	Condition	No of participants/ age	Study design	Result(s)
Carmona-Ramirez, 2002	Recurrent RTIs work environment	N= 112 mean age of 37.9 ± 8.0 years	Open-label prospective study	Mean rate (±SD) of acute RTIs from 8.2 ± 2.1 during the previous year to 5.3 ± 2.9 at the end of the study period (p<0.001). Temporal effects not addressed
Geiser, 1983	Recurrent RTIs work environment	N= 170 16–65 years	RCT	Reduction bronchitis scores in favour of BV (median score: 2 vs. 1, p < 0.05) vs. placebo Work absenteeism not significant. No information on validation of scores
Capetti, 2013 Letter to the editor	At risk for RTI in HIV patients	N=130 35–77 years	Observational study	Compared to pre-treatment significant reduction. RTIs monitored over 6 years (lack of information regarding temporal pattern/ confounders)
Zhang, 2012	At risk for RTI autoimmune nephrosis	N= 40 patients	RCT, no blinding	No effect on nephrosis outcome RTI rates 4/6, antibiotics 0/4,duration of RTI 18/37 Statistically significant. No placebo control, results available for 31/40 pts
Li, 2004	Exacerbation Smokers, CB, moderate COPD	90 patients; 49 BV/ 41 placebo	RCT	Exacerbation incidence 3.8 ± 1.3 vs. 2.1 ± 0.8), duration (mean number of days: 39.8 ± 6.7 vs. 21.3 ± 6.1) Statistically significant
Xinogalos, 1993	Exacerbations In COPD	N=104 enrolled N=62 completed	RCT	No of acute exacerbation and severity significant reduced compared to placebo. Per protocol analysis only (N=42 drop outs)

Study first Author, year	Condition	No of participants/ age	Study design	Result(s)
Cvoriscec, 1989	Acute episodes mild CB	N= 104 age 20–69 years	RCT	BV group significant better compared to placebo with regard to duration of acute exacerbation, antibiotic treatment, % ß2-agenoist aerosol. Potential heterogeneity of both groups
Keller, 1984	Acute bronchitis in pts. with CB	N=81 No information on age	RCT	Positive effect using a 4-point scale for BV compared to placebo ($p < 0.05$) bronchitis symptoms n.s. different
Ahrens 1983 Byk Gulden Pharmazeutika	RCT in COPD Selection criteria allowed inclusion of non-susceptible subjects; reason for exclusion of participants not given	N=230 age 14–82 years	RCT, unclear if actually randomised	Significantly less frequent and sever respiratory infections in the BV vs. placebo group. High risk of bias
Christopoulos, 2014	Allergic asthma control	N=130 age 15-57 years	RCT Double-blind	Add on therapy: BV + standard therapy achieved significant better asthma control compare to placebo plus standard therapy. No information on placebo. Run-in time possibly too short.
Esposito, 2014	Recurrent RTI Insufficient information regarding case definition URTI/LRTI	N= 68 36-59 months of age	RCT, unclear if single blind. BV + inactivated flu vaccine vs. flu vaccine	Mean no. (±SD) of URTI 0.73 ± 0.49 BV vs. 2.19 ± 0.73; mean no. LRTI 0.28 ± 0.16 BV vs. 0.68 ± 0.44 (secondary endpoint, as the primary endpoint was the immunogenicity of flu vaccine)

Study first Author, year	Condition	No of participants/ age	Study design	Result(s)
Del-Rio-Navarro, 2003	Prophylaxis of RTI (patients with hypogam-maglobulinaemia)	N=43 age 3 to 6 years	RCT Double-blind	2.8 RTIs BV vs. 5.2 in the placebo group ($p<0.001$). No α-adjustment to account for multiple testing. All URTIs except 4 LRTIs (7%) in active group and 10 LRTIs (10%) in placebo group.
Maestroni, 1984	URTI	N=20 age 1–16 years	RCT, Double blind	Significant difference in incidence: URTI 9.2 (1.53/month) BV vs. 9.7 (1.61/month) placebo groups
Chen, 2017	Recurrent URTI (chronic sinusitis)	N=96 age 4-12 years	Open label, no information on randomisation	Nasal scores improved significant in BV group compared to control (no treatment) No. of nasal symptoms significant reduced in BV group after 1 year compared to control
Bitar, 2013	Recurrent tonsillitis	N=169 Age 6 mo-18 years	Retrospective non-interventional study	75.6% response
Han, 2016	Bronchitis/bronchial asthma	N=144 age 7mo-5 years	RCT Open-label	Rate and the duration of bronchitis in the BV group significant better than placebo
Lu, 2015	Prophylactic exacerbation in asthma patients	N=60 Age 5-15 years	RCT Open-label	Asthma attacks were significantly decreased in both groups (BV and placebo) compared to before therapy. RTIs were reduced only in BV group.

Study first Author, year	Condition	No of participants/ age	Study design	Result(s)
Razi, 2010	Prevention of viral RTI-provoked wheezing in children with recurrent wheezing	N=75 age 2-6 years	RCT Double-blind	BV + standard of care had significantly fewer RTIs and wheezing compared to placebo + standard of care (difference: 37.9%; p < 0.001)
Liao, 2014	Recurrent RTIs 1) (asthmatic population)	N= 62 Age 1–12 years	RCT Double-blind	Significant difference in incidence of URTIs and in incidence of LRTIs in favour of BV. About 70–80% of all RTIs were URTIs; about 20–30% were LRTIs
Studies in the treatment of acute RTI				
Heintz, 1989	RCT in Chronic rhinosinusitis	N= 284 age >16 years	RCT, unclear if actually randomised	Symptom score significantly in favour of BV, BV treated group experienced approximately half the number of infections compared to the placebo. Statistical shortcomings (e.g. no α adjustment for multiple testing). Effect mainly related to major difference on scores at mo 6. Selective exclusion of patients from analysis. Questionable clinical relevance
Czerniawska-Mysik, 1992	Control of asthma and recurrent acute bronchitis, two distinct disease entities; unclear case definition.	N=59 adults	RCT Double-blind	Compared to the year before, BV reduced the number, duration and severity of bronchitic exacerbations (p < 0.01). At 6 mo. significant improvements in favour of BV vs. placebo

Study first Author, year	Condition	No of participants/ age	Study design	Result(s)
Gomez-Barreto, 1998	Treatment and prophylaxis subacute sinusitis	N=56 Age 18 mo-9 years	RCT, Double-blind	BV + antibiotics had significantly faster and more pronounced improvement of sinusitis vs. placebo + antibiotics. BV group had fewer infections vs. Placebo (1.56 ± 0.30 vs. 2.22 ± 0.43). Flow of participants unclear
Zagar, 1988	Treatment chronic sinusitis	N=51 Age 4-12 years	RCT, Double-blind. Patient selection, randomization and placebo not described	Significant reduction of cough, nasal discharge, nasal congestion in BV group vs. placebo by day 15; effect was maintained throughout the treatment period
Berber, 1996	Treatment RTI	N=587 paediatric	open-label, uncontrolled	time to improvement and cure significantly reduced compared to previous control period ($p < 0.001$) by 44.4% (6.77 ± 4.42 vs. 3.76 ± 2.18 days) and 37.9% (11.86 ± 8.41 vs. 7.36 ± 4.93), respectively.
Liu, 2017	Bronchiolitis	N=124 age 2 mo-2.5 years	RCT Double-blind	Therapeutic rate was higher in the BV group vs placebo (59 patients, 95% vs. 52 patients, 84%) p=0.040). Patient characteristics and concomitant treatment not provided

The published review articles provided related to Broncho-Vaxom and other immunostimulants or immunomodulators in children (Steurer-Stey, 2007; Rozy and Chorostowska-Wynimko 2008; Schaad, 2010, Sopo, 2011; Del-Rio-Navarro, 2012; Cardinale, 2015; Kearney, 2015; Schaad, 2016; Yin, 2018; Esposito, 2018). Four of these articles included meta-analyses (Steurer-Stey, 2007; Schaad, 2010; Del-Rio-Navarro, 2012; Yin, 2018). The studies included in the Cochrane review by Del-Rio-Navarro and colleagues have been presented above.

Discussion

Broncho-Vaxom is indicated for the prevention and treatment of RRTI in adults and children. In one MS the indication in children is limited to bacterial RURTI, while in five others it is also generally authorised as immunotherapy. Depending on MS, the paediatric indication covers children from 1 year, 6 months, or without restrictions.

None of the MAH sponsored studies in adults provided a valid proof of superiority over placebo, in view of the major limitations identified. Three studies were conducted in LRTIs and 1 smaller study in patients with haemodialysis investigated upper and lower RTI.

The MAH sponsored studies in children showing statistical superiority over placebo had either questionable statistical results and/or qualitative deficiencies as presented above.

The majority of the supportive publications included small numbers of patients and different dose regimens of BV in different ethnic groups, as well as methodological problems concerning the statistical analyses. Important information was frequently not described in the manuscripts such as patient selection, patient characteristics, primary endpoints, case definitions, randomisation, validation of scores and type of placebo, thus impeding the assessment. Information on concomitant medication (including vaccination in chronic disease patients) which may have an impact on the frequency and severity of exacerbation was also not provided in the overall majority of studies. Comparisons with anamnestic pre-treatment conditions in several studies may be problematic and may introduce bias.

Taken together the MAH's sponsored studies in children and some of the supportive studies suggest some limited evidence as a prophylaxis for RTI.

The studies in children and adults with diverse (sinusitis, RTI, bronchiolitis, bronchitis, asthma) acute events at study entry present major methodological limitations (e.g. open and uncontrolled (Berber), low sample size (Zagar, Czerniawska-Mysik, Gomez-Barreto, Liu, Heintz), unclear patient selection (Zagar), case definition (Czerniawska-Mysik), patient allocation, treatment and exclusion from study analysis (Gomez-Barreto, Heintz), randomisation procedure (Zagar, Heintz) and/or lack of patients characteristics (Liu), concomitant treatment (Liu) and/or lack of α adjustment for multiple testing (Heintz). Further considering the different diseases included the total sample size is low comprises (327 paediatric and 173 adult patients treated with Broncho-Vaxom). These are not considered to provide robust evidence that Broncho-Vaxom can effectively be use as immunotherapy/supportive therapy/adjuvant treatment of an acute RTI. The MAH clarified that the intention behind the treatment indication was to indicate that Broncho-Vaxom can be initiated during the acute phase of an upper RTI in order to prevent the complications of the upper RTI, including, for example, the spreading of the infection to the lower respiratory tract and to prevent further infections.

The MAH also clarified that Broncho-Vaxom was not specifically indicated in the treatment or prophylaxis of pneumonia. No evidence demonstrating a direct preventive effect of Broncho-Vaxom against pneumonia was available. The MAH proposed to include a statement in the SmPC to recommend against the use in the prevention and treatment of pneumonia in view of the absence of data.

2.2.7. Ribomunyl

The MAH submitted the results from 10 double-blind, placebo-controlled RCT, in 955 patients treated with Ribomunyl and 960 patients treated with placebo, as well as a review of published RCT and meta-analyses. The MAH's sponsored studies, included exclusively children <15 years of age and focused on patients with recurrent ear, nose and throat (ENT) infections/URTI, except for *MR14*, which included

patients with bronchial infections. The primary criterion in almost all the studies was the number and duration of ENT/URTI episodes, or specifically of nasopharyngeal episodes.

Study *MR11* (September 1982 – May 1983) included 136 patients aged 2 to 14 years (mean: 7 years) suffering from recurrent ENT infections: otitis (>25%), sinusitis, rhinopharyngitis (50%), rhinosinusitis or pharyngitis, and with a history of at least 4 episodes of secondary infections over the 12 months prior to study entry (mean 6-7 episodes). At 6 months, amongst the 87 assessable cases (i.e. without major protocol deviation or premature withdrawal [corresponding to 64 % of enrolled patients]) the mean number of infectious episodes was 4.04 ± 4.15 in the active group and 5.38 ± 3.70 in the placebo group ($p<0.01$). The mean duration of infections was 25.5 ± 18.4 days vs. 35.0 ± 27.9 days ($p<0.02$). During this 6-month period, 38% presented with ≤ 2 episodes vs. 18% ($p<0.05$).

Study *MR12* (January 1986 – June 1986) included 111 patients aged <5 years (mean: 4 years). Patients had suffered from at least 3 episodes of ENT infection over 12 months prior to study entry (mean: ~6.7- 7 episodes). The aim was to demonstrate prevention of ENT. At 6 months, 87 cases were assessable. The mean number of infectious episodes was 3.24 ± 2.12 in the active group vs. 4.90 ± 4.25 in the placebo group ($p=0.18$). At 3 months, the mean number of infectious episodes was 1.94 ± 1.09 in the active group vs. 3.08 ± 2.48 in the placebo group ($p=0.05$). The mean duration of infections was 18.2 ± 22.8 days in the active group vs. 30.2 ± 12.5 days in the placebo group ($p=0.027$). The MAH stated that a significant centre-treatment interaction was observed. These results should therefore be considered with caution and this study remains non-conclusive.

Study *MR21* (November 1988 – November 1989) included 114 patients aged 3 to 15 years (mean: 7 years). The main criterion used in this study was a semi-quantitative score based on several parameters, which does not allow drawing meaningful conclusion with regards to efficacy.

Study *MR14* (Winter 1989 - 1990) included 172 patients, aged 3 to 12 years (mean: ~5.5-6 years). Patients were suffering from recurrent ENT infections: otitis (7%), sinusitis/rhinosinusitis (13%), tonsillitis or pharyngitis (13%) or bronchitis (53%) and had a history of at least 3 episodes of secondary infection over 12 months prior to study entry (mean: ~6-6.3). At 6 months, 156 patients were assessable. The mean number of infectious episodes was 1.70 ± 0.2 in the active group and 2.50 ± 0.2 in the placebo group ($p=0.009$), and the mean duration of infections was 14.3 ± 13.0 days vs. 20.8 ± 17.0 days in the placebo group ($p=0.018$), showing a significant beneficial effect of the product in comparison with placebo.

Study *MR15* (September 1989 – June 1990) included 64 patients aged <5 years (mean: 3 years), with 31% <2 years. The study evaluated efficacy of Ribomunyl tablets in the prophylaxis of recurrent and secondary infections in children aged less than 5 years (Sept 1989 – Jun 1990). Patients had a history of at least 5 episodes of ENT infection over the 12 months prior to study entry, or 3 episodes over the last 6 months (mean: 6 episodes). At 6 months, 61 patients were assessable. The mean number of infectious episodes was 3.39 ± 0.38 in the active group and 5.56 ± 0.39 in the placebo group ($p<0.001$). The mean number of days of antibiotic treatment was 18.8 ± 17.9 days vs. 27.9 ± 10.5 days in the placebo group ($p=0.017$).

Study *J0022X 97 ST 401* (September 1997 – June 1998) included 394 patients aged ≤4 years (mean: 2.5 years). Patients were suffering from recurrent nasopharyngitis, with a history of at least 6 episodes (of which 3 were medically recorded) of infection over the 9 months prior to study entry (mean: 7.8 episodes). History of serous otitis was present in 25% of the patients. The aim of the study was to demonstrate prevention of recurrent nasopharyngitis. At 6 months, 387 patients were assessable (350 in the Per Protocol Population (PPP)). The mean number of nasopharyngitis episodes was similar in both groups: 3.2 ± 1.7 in the active group vs. 3.1 ± 1.7i n the placebo group (not significant [NS]).

The duration of nasopharyngitis episodes was 18.3 ± 13.0 days in the active group vs. 15.2 ± 12.0 days in the placebo group (NS). There was no proof of superiority versus placebo.

Study *J0022X 98 ST 401* (September 1998 – June 1999) had a similar design to study *J0022X 97 ST 401* and included 366 patients aged ≤4 years (mean: 2.2 years). At 6 months, 362 patients were assessable (328 in the PPP) and the cumulative number of rhinopharyngitis episodes was similar in both groups: 2.4 ± 1.6 in the active group vs. 2.5 ± 1.7 in the placebo group (NS). The mean cumulative duration of rhinopharyngitis episodes was 17.0 ± 14.0 days in the active group vs. 17.4 ± 11.4 days in the placebo group (NS). There was no proof of superiority vs. placebo. The MAH stated that the analysis showed a major country effect.

Study *J0022X ST 402* (October 2003 – June 2004) was conducted in a subgroup of the targeted population, i.e. 144 children with a history of atopy aged between 3 and 5 years (mean: 3.7 years). Patients had suffered from at least 3 ENT infections within a period of 6 months in the year prior to inclusion (mean: 3.9 episodes). At 6 months, 144 were assessable (97 in PPP). At 6 months, the cumulative number of ENT episodes per child was too low in both groups: 1.2 ± 1.3 in the active group vs. 1.2 ± 1.2 in the placebo group, to enable demonstration of a difference (NS). The mean cumulative duration of ENT episodes was 8.3 ± 10.1 days in the active group vs. 9.0 ± 10.4 days in the placebo group (NS). There was no proof of superiority versus placebo.

Study *J0022X ST 403 (LF-PF-1;* August 2008 – December 2009) included 164 patients aged between 2 and 5 years (mean: 3.8 years). At 6 months, 158 were assessable (155 in the PPP). The mean number of ENT episodes over the previous year was 6.8 episodes. At 6 months, the mean duration of ENT episodes was similar in both groups, 5.40 ± 3.74 days in the active group vs. 5.43 ± 3.06 days in the placebo group (NS). The number of episodes in 6 months was 2.00 ± 1.51 days vs. 1.82 ± 1.18 days (NS). There was no proof of superiority placebo versus placebo.

Study *J0022X ST 302 (CLEARI*; September 2013 – October 2016) is the most recent and well design study with this product. It investigated the prevention of recurrent Upper Respiratory Tract Infections (RURTI) in children with a high risk of recurrence (Sept 2013 – Oct 2016). In Year 1 of the study, 994 patients (aged 3-4 years) known for recurrent URTIs in the previous year were included for observation. In many of the previous studies, inclusion of children had been based on parental reporting of the patients' URTI episodes, which were not always confirmed by medical assessment. In this study disease characteristics were based on consistent measures. Of these patients, 254 (having suffered at least 6 URTI episodes medically confirmed, with a maximum of 18, during the 1-year observational period of the study were randomised to receive Ribomunyl (active group) or placebo in Year 2. Patients received treatment for the first 6 months of Year 2 and were followed for another 6 months to evaluate URTI episodes. All 254 patients were included in the Full Analysis Set (248 patients were included in the PPP). At randomisation (Year 2), the mean age of patients was 4.2 years (ranging from 3-5 years). The mean (standard deviation [SD]) number of URTI episodes experienced per patient during Year 1 was 6.6 (0.9) in the active group and 6.6 (1.0) in the placebo group. All patients in both the active group and placebo group experienced 6 or more medically confirmed episodes of URTIs. The adjusted mean ± standard error (SE) number of URTIs in Year 2 was 2.51 ± 0.20 in the active group vs. 2.82 ± 0.18 in the placebo group. No statistically significant difference was observed between treatments on the FAS (p=0.210). Supportive analysis on the PPP and further sensitivity analyses confirmed the non-significant results obtained in the FAS. Most of the secondary efficacy analyses (i.e. severity, otitis media infections, and use of antibiotics, NSAIDs or corticosteroids) did not show any significant difference between treatments.

The review of published RCT and meta-analyses provided by the MAH included two publications by Mora and colleagues in 2002 and 2010 in prevention of otitis media, recurrent acute adenoiditis (RAA)

showing some effects in favour of the treatment group and a third one in 2012 in adults with pharyngolaryngeal reflux disease (PLRD) showed significant improvement ($p<0.05$) in the Ribomunyl group for almost all the variables analysed. Three meta-analyses (Bellanti 2003, Boyle 2000 and Del-Rio-Navarro, 2006) found that Ribomunyl compared to placebo: reduced the number or URTI and LRTI in children and adults, reduced the number of RTI and antibiotics courses in children and adults and reduced the number of acute RTIs in children, respectively. Del-Rio-Navarro noted that the quality of trials included in the meta-analysis was considered as generally poor and there was a high level of statistical heterogeneity.

Discussion

Ribomunyl is indicated for the prophylaxis of RURTI in children above 2 or 6 years old depending on the presentation, and of recurrent surinfections in chronic bronchitis in adults.

The data do not demonstrate a significant benefit in children and adults in the prophylaxis of URTIs. Indeed, most clinical studies were associated with several methodological limitations and therefore the positive results observed in some of these studies cannot be relied upon. In addition a recent well-designed randomised controlled trial in children failed to demonstrate a benefit of Ribomunyl over placebo (CLEARI).

The meta-analyses submitted included clinical trials of generally poor quality and there was a high level of statistical heterogeneity. Therefore, these are not considered either to provide proof of efficacy.

Of note, having already stopped the manufacturing of the biomass, the MAH decided to stop as of 31 December 2017 placing the product on the market for commercial reasons and is progressively withdrawing its MAs. MAs were withdrawn in one MSs during this procedure and the MAs remaining in the seven other MSs are planned to be withdrawn sequentially after the expiry of the last batches on the market. All MAs were planned to be withdrawn by June 2020.

2.2.8. Polyvaccinum

The MAH submitted the results from 3 studies with the nasal drops and 2 studies with the suspension for injection. Summary information was submitted for a further 6 studies with the nasal drops and 2 with the suspension for injection. In addition, it is noted that a double blind, placebo-controlled, RCT for which no results are available is ongoing with the nasal formulation in 80 children with allergic rhinitis or allergic rhinitis and conjunctivitis caused by grass and cereal pollen (Emeryk).

Table 5. Overview of studies conducted with Polyvaccinum

Study first Author, year	Design	Patient No. (Investigational product/ control) and patient age	Condition	Primary endpoint	Case definition and duration of follow up	Result(s)
Szczypiorski, 1974, 1976, 1977	no double blind, non-randomized CT	Polyvaccinum nasal drops, 3 study parts N= 234	recurrent or chronic respiratory tract	Recurrence and overall effect	No information. FU: from 6 months	Improvement health status 76 - 86 %; morbidity rate of

Study first Author, year	Design	Patient No. (Investigational product/ control) and patient age	Condition	Primary endpoint	Case definition and duration of follow up	Result(s)
	Only descriptive analysis, clinical data were provided	investigational/ 15 control (N=381 for the long term follow up). 7 months to 16 years of age	diseases		to 8 years	treated patients significantly lower
Lewandowska, 1968	non-randomized uncontrolled post-marketing study	Polyvaccinum suspension for injection and Lantigen B N=500 children N=350 bronchial asthma; N=150 chronic spastic bronchitis. 6 months to 14 years of age	bronchial asthma and chronic spastic bronchitis	efficacy and safety clinical study	No information. FU 6 months to 5 years	Good clinical response observed in 81 % of patients with bronchial asthma and in 91 % of patients with obstructive chronic bronchitis
Sawiełajc - unpublished	Uncontrolled, single arm, open study Study Report, with descriptive data	Polyvaccinum suspension for injection N=50 patients 3 - 6 years of age	obstructive bronchitis	cell-mediated and humoral immunity	Recurrent: frequencies of six or more times a year (6-10 times)	very good and good clinical response, n= 35 poor clinical response or no response, n=15 No exacerbation of

Study first Author, year	Design	Patient No. (Investigational product/ control) and patient age	Condition	Primary endpoint	Case definition and duration of follow up	Result(s)
						disease
Ziuzio, 1994	Open, not randomized Differentiation between products not clear	Bronchovaxom, IRS-19 and Polyvaccinum nasal and subcutaneous/placebo 160 children 80/80 5-15 years of age	nasal and sinus bacterial allergy	improvement or regression of clinical manifestations,	No information	Statistically significant results vs. untreated control

Szczypiorski (1973, 1976 and 1977) and Chmielewska (1975) also published investigations of diverse immunological parameters in. In these studies increases of IgA antibodies in blood serum and nasal secretion were detected. The clinical relevance of these findings remains is unknown.

None of the 8 open non-randomised studies with polyvaccinum suspension for injection submitted were considered of clinical significance (Nowak, 1967; Sielużycki, 1968; Kowal, 1969; Chyrek-Borowska, 1971; Sośnierzowa 1971; Pietruska, 1971; Mirska-Brajczewska, 1976; Przybył-kiewicz, 1980).

Discussion

Polyvaccinum is indicated as nasal drops for prophylactic and therapeutic treatment of long-lasting, chronic and recurrent URTI in children and adults and as injectable form for prophylactic and therapeutic treatment of RRTI in children and adults.

Studies were only performed in children and none were placebo-controlled, double blind RCT. Serious limitations to the design of the studies have been identified such as: unclear study objectives and uncertainties about diagnoses, case definitions, patient selection and ascertainment in controlled studies, concomitant treatment, as well as analysis of data (only descriptive analysis was performed).

Therefore, the positive results reported should be interpreted with caution and cannot constitute robust evidence to establish efficacy in the authorised indications.

2.3. Data on safety

The MAH provided an overview of all suspected ADR reports with their products, with a particular focus on immunological adverse reactions.

For most products the number of reports is very low, which considering the patient exposure suggests a possibly important underreporting. Overall no new significant information was identified from this data. The below cases are noted however.

Respivax: a serious spontaneous report for Respivax 50 mg of multiple sclerosis relapse.

Ismigen: two cases of Guillain-Barré Syndrome (GBS), thereof one with fatal outcome, for both of which the causality remains unclear.

Broncho-Vaxom: a case of toxic epidermal necrolysis in a 5-year old patient for which the causality remains uncertain due to other confounding factors.

Ribomunyl: a fatal case in a 16-month-old further to for which the causal relationship with Ribomunyl tablets was considered as probable due to suggestive re-challenge and classified as due to an allergic drug induced fever. It is not unexpected that the antigens in the formulation may induce pro-inflammatory and pyrogenic cytokines which may result in individual cases of high fever and serious hypersensitivity reactions. Pyrexia and urticarial are the most reported terms post-marketing.

2.4. Quality aspects

2.4.1. Formulations in children age 5 years and younger

The CHMP reviewed the appropriateness of the formulations of the products authorised in the paediatric populations below 6 years old, considering the EU Guideline on the pharmaceutical development of medicines for paediatric use and the EMA reflection paper formulation of choice for the paediatric population.

Luivac

Luivac is a cylindric, slightly convex white tablet (diameter of 6.8 mm and a thickness of 3.35 mm) to be taken whole on an empty stomach. The MAH stated that the paediatric indication includes children from 4 years. The age cut-off is also in line with the age category studied in the two double-blind, placebo-controlled RCTs in children. However, this age cut off is not explicitly mentioned in all EU product information. The MAH did not discuss the possibility of underreporting of tablet crushing or dispersing to facilitate intake. Data on accurate dosing in case of breaking the tablet have not been presented. It is recognised that tablets of such dimensions may be difficult to swallow for young children; nevertheless this may be achieved with training (Mistry and Batchelor, 2017). The product information should be amended to clarify in all the product information that the product is only indicated in children from 4 years old.

Respivax

Respivax is a tablet for use in children from 3 years of age. The MAH did not discuss the appropriateness of the pharmaceutical formulation of Respivax 25 mg tablets for children aged 3-5 years. As per the product information, Respivax is not recommended for children younger than 3 years. The MAH is therefore asked to perform an acceptability study for children 3-5 years of age. The test may be part of the requested paediatric study.

Lantigen B

Lantigen B is a suspension for oral drops for use in children without age restrictions in three MS and in children from 3 years of age in a fourth MS. The pharmaceutical formulation is considered appropriate in the paediatric population below 6 years of age.

Buccalin

The diameter of the Buccalin film-coated tablet is 9.0 – 9.2 mm to be swallowed whole. In one MS Buccalin is indicated in children from 6 months of age onwards, whilst no age restriction is included in

the product information in the other MS where it is authorised. Children may not be able to swallow tablets of this size, for this reason in they are discouraged in children between 2 and 5 years of age (Mistry and Batchelor, 2017). Although, in clinical studies in young children no administration problems were mentioned, the size of the tablet may be too large for young children. No data have been presented regarding accuracy of dosing in case of breaking/crashing the tablet. According to the MAH, that no issues were identified in this regard in paediatric clinical studies as well as post-marketing. No acceptability study has been conducted so far. As the MAH is planning to conduct a randomized, controlled clinical trial in children 2 years and older, the acceptability study in young children 2-5 years of age may be studied within this clinical trial. However as the formulation is unsuitable for children 2 years of age and younger, the paediatric indication should be restricted to children ≥ 2 years of age.

Ismigen

Ismigen sublingual tablet is a non-coated tablet (disintegration and dissolution of the tablet under the tongue) authorised in one MS in children from 3 years of age. Although, the tablet disintegrates quickly, it is questionable whether the sublingual administration is suitable in young children without specific training. Thus, the MAH is asked to preform and acceptability study for children 3-5 years of age. This could be performed as part of the request clinical trial.

Broncho-vaxom

Broncho-Vaxom is authorised under two pharmaceutical forms for children: hard capsules of 3.5 mg bacterial lysate and granules in sachet of 3.5 mg bacterial lysate. Depending on MS, the paediatric indication is in children from 1 year (5 MS), 6 months (9 MS), or without restrictions (2 MS). The hard capsules formulation is available in all MS where Broncho-vaxom authorised, while the granules in sachet formulation is available in most but not all these MSs.

The granules in sachet, are to be mixed with liquid before administration, while in the case of the hard capsules, if the patient has difficulties in swallowing them, the product information recommends opening the capsules and swallowing the contents with liquid. A study designed to evaluate the risk of under-dosing further to the opening of the capsules showed that accurate single dose preparation is ensured. Therefore, both pharmaceutical forms intended to be used for children are suitable for this patient population.

Ribomunyl

Ribomunyl is authorised as two pharmaceutical forms: tablets indicated for children above 6 years, and granules for oral solution for children above 2 years. The formulations are appropriate to the indicated paediatric population.

Polyvaccinum

Polyvaccinum is authorised as nasal drops in children from 6 months of age and suspension for injection in children from 2 years of age. The results of a questionnaire in 261 children under 5 years of age out of 980 patients (26.6%) revealed no problems with the nasal drops. Further, up to 17 August 2018 the MAH received a total of 1 ADR (serious) for Polyvaccinum suspension for injection, and 15 non serious ADRs after Polyvaccinum mite nasal drops administration at children at 5 years of age or below. However no formal acceptability study was performed. The suspension for injection may cause unnecessary pain in young children. The MAH is asked to perform an acceptability study for the suspension for injection in parallel or within the planned paediatric study.

2.4.2. Excipients

Both pharmaceutical form of Polyvaccinum contain phenol. Phenol is classified in the EU as a potential mutagen on the Substance evaluation list of the Community rolling action plan of the European Chemical Agency. An EU Risk Assessment Report under Council Regulation (EEC) No 793/93 concluded in 2006 that there is a need for limiting the risks to human health of phenol. It is noted that the CHMP adopted an opinion under article 5(3) of Regulation (EC) No 726/2004 (EMEA/CHMP/SWP/146166/2007) stating that "*in the event that CMR toxicity has been identified for an excipient, the rule is to avoid and replace this excipient. In the rare case where this would not be possible, the use of such CMR excipients in a medicinal product would only be considered after careful evaluation of the benefits of the medicinal product in the target patient population versus the potential risks*". The MAH has informed the CHMP that it will proceed to developing a formulation without phenol and register the reformulated products by Q1 2022.

3. Expert consultation and other data

The CHMP consulted the anti-infective scientific advisory group (SAG) which provided advice on a number of issues.

The experts were united in their view that on basis of the data available at present, it was not possible to differentiate the activity between the products of the different MAHs. It was also deemed unfeasible to extrapolate the available evidence to indications and populations for which no product specific data was available. Likewise, the experts opined that it would be difficult to group all RTIs together. Evidence obtained for URTIs cannot be extrapolated to LRTIs and vice versa. The experts also considered it not possible to extrapolate data obtained from prophylactic setting to the treatment setting and vice versa. Similarly, extrapolating results between adults and children was not considered feasible as risk factors for multiple infections in children are differing from those in adults. As such, these populations cannot be compared and if included in a same trial, this would require a proper stratification.

Therefore, and based on the evidence available, the experts agreed that the data indicate some efficacy of these products in the prophylactic setting only in relation to URTIs, as a secondary prevention, for populations at increased risk (i.e. suffering multiple bouts of URTI). However, considering the limitations of the available data, the experts were of the view that further data should be generated in order to confirm the efficacy of the products in this setting.

The experts agreed that a phase IV trial could be most useful in order to further characterise the benefits and risks for prophylaxis of URTIs with bacterial lysate medicinal products. In view of the different compositions of such bacterial lysates, it was recommended that a separate study be conducted for each product. The key elements of such trials should include the following;

- a sufficient sample size and stratification according to sample size

- a clear definition of underlying risk factors

- endpoints: a limited choice could be contemplated as primary endpoint e.g. reduction in the number of infection episodes in a predefined time period (e.g. one year); reduction in severity of infections.

- as a minimum the vaccination status of participants should be documented or preferably estimated by measuring respective level of protecting antibodies at the beginning of the study.

- duration of follow-up: at least 1 year after prophylactic use would be advisable

- cause of URTIs should be revealed and documented by appropriate microbiological diagnostic measures (bacteria, viruses)

In addition a third party submitted the study report of the AIACE (Advanced Immunological Approach in COPD Exacerbation; Braido, 2015) study together with two experts' opinions on the study results. This submission did not provide additional information to that presented by the MAHs.

4. Benefit-risk balance

Bacterial lysates-based medicinal products contain several strains of inactivated whole bacteria/bacterial lysates/bacterial fractions claimed to stimulate the immune system to recognise and fight infections. Eight medicinal products containing six different combinations of bacterial strains' lysates currently hold marketing authorisations for use in respiratory conditions in EU MS. The products have different names in the MS and whilst the most common name is used herein it should be understood as applying to all associated names. Bacterial lysates are approved in EU member states under a broad spectrum of indications that can generally be categorised as prophylaxis and treatment of URTIs and LRTIs in adults and children.

Respiratory tract infections may be differentiated in upper and lower respiratory tract infections. Upper respiratory tract infection (URTI) is a non-specific term used to describe acute infections involving the nose, paranasal sinuses, pharynx, and larynx. The prototypic URTI is the common cold. URTI occur commonly in both children and adults and is a major cause of mild morbidity. Lower respiratory tract infection (LRTI) is a broad description of a group of disease entities, encompassing acute bronchitis, pneumonia and exacerbations of chronic lung disease.

The analysis of the scientific data concerning bacterial lysates used for the prophylaxis and treatment of RTI was not able to elucidate the mechanism of action of these products. The composition, the manufacturing, the formulation, the administered dose, the treatment schedule and the route of administration of different bacterial lysates available in human therapy are heterogeneous. It remains unknown whether these differences translate into different clinical effects of the medicinal products; this conclusion was also supported by the scientific advisory group expert group meeting on anti-infectives (SAG AI).

Luivac is indicated for the prophylaxis of recurrent respiratory tract infections (RRTI) in adults and children from 4 years of age. In one MS, the paediatric indication is restricted to recurrent upper RTI (RURTI). Three double-blind RCTs conducted in children and adults showed the statistically significant superiority of Luivac over placebo with regards to a non-validated severity score used as primary endpoint, thus precluding conclusions as to the clinical relevance of the results. In a fourth double-blind placebo controlled RCT conducted in adults only, the background infection rate was very low and superiority over placebo was shown. It is noted that the authors of a review article on immunomodulators for the prevention of RTI in children (Cardinale, 2015) concluded that no sufficient evidence for the efficacy of Luivac in the paediatric field was available. No patient with COPD or chronic bronchitis appears to have been included in the available studies. The safety information from both clinical trials and pharmacovigilance data was in line with the known safety profile, as described in the product information; rare hypersensitivity/allergic reactions have been reported.

Respivax is indicated for the prophylaxis and treatment of chronic and recurrent RTI in adults and children from 3 years of age. No robust study was conducted for Respivax. Favourable effects were reported from a small placebo controlled study and 8 observation uncontrolled studies, all suffering from serious methodological issues. Overall, one adverse drug reaction (ADR) with no evaluation of causality was reported for Respivax, which is strongly suggestive a serious under-reporting.

Lantigen B is indicated for the prophylaxis and treatment of RURTI or bacterial URTI in adults and children, as prophylaxis of RRTI in adults and URTIs in children or for the prevention of RRTI in adults and children from 3 years of age. Favourable effects of Lantigen B in the prophylaxis of RTI were observed in adults and children in a number of old studies, with methodological limitations. More recent studies with more robust design report conflicting results as one study failed to show a statistically significant effect over placebo in adults and in children whilst the statistically significant results of the other study conducted in adults only should be interpreted with caution in view of the noted methodological deficiencies (Braido, 2014). A meta-analysis reporting a favourable effect had also a number of limitations and the MAH plans to revise it. No study evaluating the effect of Lantigen B in the treatment of RTIs was identified. Only a few ADRs have been collected over the last 12 year which may indicate serious under-reporting.

Buccalin is indicated for the prophylaxis of RRTI in adults and of bacterial RURTI in children older than 6 months or for the prophylaxis of bacterial RTI without age limits. A recent RCT provided limited evidence for some positive effects in the prophylaxis of RTIs in adults (statistically significant improvement in the number of days with RTI); the clinical relevance of these results is questionable considering that no superiority over placebo was observed for important secondary endpoints. Limited evidence of efficacy in the prophylaxis of RTIs in children is mainly based on a retrospective study. No robust study was conducted in the prophylaxis of RTIs children; however, a retrospective cohort study and two small RCT provide some limited evidence of efficacy. Overall 9 ADRs were recorded over the last 16 years which may indicate serious under-reporting.

Ismigen is indicated in for the prophylaxis of RRTI in adults and in some MS for the treatment of acute, subacute recurrent or chronic RTI as well as in one MS in children from 3 years of age. A small double-blind placebo-controlled RCT and some supportive studies with methodological limitations provide some evidence of efficacy of Ismigen in the prophylaxis of URTIs in adults. Conflicting results were obtained from two double-blind, placebo-controlled RCT evaluating Ismigen in the prophylaxis of LRTI in adults. No robust study was conducted in the prophylaxis of RTIs in children, however positive results were shown in a few small open studies. No study evaluating the effect of Ismigen in the treatment of RTIs was identified. The review of the safety profile of Ismigen confirmed the known risk serious hypersensitivity reactions. Two cases of Guillain-Barre syndrome were recorded for which causality remains unknown due to a lack of information and without proper age-stratified observed versus expected analysis.

Broncho-vaxom is indicated in for the prevention and treatment of RRTI in adults and children. In one MS the indication in children is limited to bacterial RURTI, while in five others it is also generally authorised as immunotherapy. Depending on MS, the paediatric indication covers children from 1 year, 6 months, or without restrictions. Whilst most double-blind, placebo controlled, RCTs and supportive studies reported positive effects of Broncho-Vaxom these are not considered to provide robust evidence of efficacy in adults of children, in view of the methodological limitations noted. The review of the safety profile of Broncho-Vaxom confirmed the known risk serious hypersensitivity reactions, in particular two life-threatening cases of anaphylactic reactions and one report of toxic epidermal necrolysis in a 5 year old for which the causality remains uncertain were noted.

Ribomunyl is indicated for the prophylaxis of RURTI in children above 2 or 6 years old depending on the presentation, and of recurrent surinfections in chronic bronchitis in adults. Conflicting results were observed in all double-blind, placebo-controlled, RCT which were associated with methodological limitations. A recent well-designed, double-blind, placebo-controlled, RCT in children failed to demonstrate any significant effect of Ribomunyl in the primary (i.e. number of URTI) and most secondary endpoints. A fatal case of allergic drug induced fever was noted after re-exposure.

Polyvaccinum nasal drops are indicated for the prophylaxis and treatment of RURTI in adults and children from 6 months old and suspension for injections are indicated for prophylactic and therapeutic use or adjunctive treatment in case of long-lasting, chronic and recurrent RTI in adults and children from 2 years of age. No robust study was conducted for Polyvaccinum and no data in adults was identified. A few studies with significant methodological limitations reported on favourable results with the suspension for injection and the nasal drops. Post-marketing reports concerned mostly injection site reactions for one presentation and "flu like" signs and symptoms for the other one. A serious under-reporting is suspected.

Overall the data available are of poor quality and do not provide robust evidence of the efficacy of these products in their authorised indications. Limited data provides some evidence of efficacy in the prophylaxis of respiratory infections to different extents depending on products and on age groups. More recent well designed RCTs (e.g. AIACE, ACASP, CLEARI) failed to demonstrate efficacy of Ismigen in adults with COPD, Luivac in adults mainly with URTI and Ribomunyl in children with URTI, albeit in some these studies the background infection rate was very low, thus complicating the interpretation of the results. The SAG AI was of the view that extrapolation of clinical effects of the medicinal products in prophylaxis of URTI to LRTI and vice versa is not scientifically justified because upper and lower RTI represent different disease entities. Of note, the Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases does not recommend oral bacterial lysates for the management of adult LRTI (Woodhead, 2011). The SAG AI considered that the data indicate some efficacy of these products in the prophylactic setting only in relation to URTIs, as a secondary prevention, for populations at increased risk. The CHMP noted that whilst serious LRTI can be clearly distinguished from URTI (e.g. exacerbation of asthma, pneumonia), numerous URTI may lead to involvement of the bronchi. The CHMP also noted that whilst some studies suggest that the positive effects observed were mainly related to URTIs, for the majority of studies it was not possible to differentiate between the effects related to the prophylaxis of URTIs and that related to the prophylaxis of LRTIs. Therefore, no definite conclusion could be drawn on the efficacy in the prophylaxis indication based on the available data.

No new safety risk was identified and the safety profile remains overall unchanged for these products. It is noted that serious hypersensitivity reactions may occur. The CHMP noted that underreporting is probable.

The CHMP considered the benefit-risk balance of the bacterial lysates unchanged in the prophylaxis setting with regard to their authorised subsets of recurrent RTIs. However considering the lack of robust evidence, the conduct of phase IV placebo-controlled, double-blind, multicentre, RCTs according to agreed protocols in order to further characterise the efficacy and safety in their authorised indication(s) should be imposed on the MAs of these products. This was also supported by the SAG AI. The MAHs are encouraged to seek scientific advice to the relevant competent authorities to design these studies.

For Respivax, Lantigen B, Ismigen and Polyvaccinum, no data was identified in the treatment of RTIs, while for Broncho-Vaxom the data available present major methodological limitations and represented a small sample size. It was also agreed that the treatment indication was not intended to indicate a curative effects but rather to that the products could be used to prevent complications of RTIs or further infections. The SAG also considered that extrapolation of clinical effects in prophylaxis of upper and lower RTI to treatment of these infections, and vice versa was not scientifically justified, which was agreed by CHMP. Considering these clarifications and the absence of data showing a clinical effect in treatment setting, the CHMP was of the view that the treatment indication does not appropriately reflect the intended use of the products and any reference to a treatment effect should be deleted.

Some indications currently specify that the products should be used for bacterial infections only; however, there are no grounds for this claim as in the available studies no diagnosis of the pathogen was performed. Further, considering the severity of pneumonia, the CHMP considered that a warning should be added in the SmPC of all products with the unspecified RTI indication to recommend against the use in the prevention of pneumonia in view of the absence of data demonstrating the efficacy for the prophylaxis of this type of infection.

Having reviewed the appropriateness of the formulations and pharmaceutical forms for use in the authorised paediatric populations up to 5 years of age, the CHMP considered that acceptability studies in children below the age of 5 years should be performed for Respivax, Buccalin, Ismigen, Polyvaccinum suspension for injection. The minimal age group for which Luivac can be used (from 4 years of age) should be explicitly stated across all EU MS PIs. Further in view of the size of the Buccalin tablet, it should not be used in children below 2 years of age; the indication should be revised accordingly.

Finally the CHMP noted that Polyvaccinum-containing products contain phenol, an excipient that should be avoided. The MAH will register reformulated products without phenol by Q1 2022.

In conclusion, the CHMP considers the benefit-risk balance of bacterial lysates based products for use in respiratory conditions unchanged in the prophylaxis setting with regard to their authorised subsets of recurrent RTIs, provided their efficacy and safety is further characterised by Q1 2026 through the conduct of phase IV double-blind, multicentre, RCTs in this indication, and provided the agreed changes to the product information are implemented.

5. Risk management

5.1. Clinical trials

Each MAH shall conduct and submit for their medicinal product(s) the results of placebo-controlled, double-blind multicentre RCTs according to agreed protocols in order to further characterise the efficacy and safety, of their bacterial lysate based product(s) in their authorised indication(s). The study population should be representative for the authorised indication(s). Results shall be submitted to the National Competent Authorities for assessment by Q1 2026.

The primary objective should be the reduction of the number of respiratory tract infections. In order to ensure the study population enrolled will be representative for the authorised indication, a run-in phase is recommended. The CHMP considered extensively whether these studies should be conducted jointly by the MAHs. As discussed, it still remains uncertain whether the known differences between these medicinal products translate into different clinical effects; therefore any joint studies would need to be very large in order to be sufficiently powered to allow concluding on the efficacy and safety of the individual products in their authorised indications. This would increase complexity (e.g. randomisation, blinding, conduct of studies, statistical analysis), possibly generate delays and in turn increase the risk for the results of the studies to be inconclusive. Therefore, in order to ensure meaningful data is generated for each product without undue delays, CHMP recommended that separate studies be conducted for each product.

The MAHs are encouraged to seek scientific advice to the relevant competent authorities.

5.2. Amendments to the product information

The CHMP considered that amendments to sections 4.1 and 4.4 of the SmPC were necessary to include the conclusions of this review.

The indication was restricted to the prophylaxis of RRTIs in the currently authorised subsets of that indication.

After review of the adequacy of the formulation and pharmaceutical form, the minimal age of children for which Buccalin is indicated was raised, and that for which Lantigen B is indicated was clarified across MS.

Further, a warning that the use of these products is not recommended in the prevention of pneumonia was also included in view of the lack of clinical data.

The Package Leaflet was amended accordingly.

5.3. Pharmaceutical aspects

Acceptability studies in children below the age of 5 years should be performed for Respivax, Buccalin, Ismigen, Polyvaccinum suspension for injection. The studies may be performed as part of the imposed RCTs or separately.

The MAH of Polyvaccinum will register reformulated products without phenol by Q1 2022.

6. Condition(s) to the marketing authorisations

The marketing authorisation holders shall complete the below condition, within the stated timeframe, and competent authorities shall ensure that the following is fulfilled:

Each MAH shall conduct and submit for their medicinal product(s) the results of placebo-controlled, double-blind multicentre RCT(s) according to agreed protocols in order to further characterise the efficacy and safety, of their bacterial lysate based product(s) in their authorised indication(s). The study population should be representative for the authorised indication(s). The protocols should be agreed with the relevant NCAs.	
The clinical study report should be submitted to the relevant National Competent Authorities by:	31 March 2026

7. Grounds for Opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for bacterial lysates based medicinal products for use in respiratory conditions.
- The CHMP considered the totality of the data submitted for bacterial lysates based medicinal products for use in respiratory conditions. This included the responses submitted by the

marketing authorisation holders in writing and during Oral Explanations, the information submitted by a third party, as well as the views expressed by the scientific advisory group on anti-infectives.

- The CHMP considered that overall the data available presents serious limitations and does not provide robust evidence of the efficacy of the products in their authorised indications. Limited data provides some evidence of efficacy in the prophylaxis of recurrent respiratory infections to different extent depending on products and on age groups. However, no definite conclusion can be drawn on the efficacy in this indication.
- The CHMP considered the lack of evidence in the treatment settings and that the treatment wording was not reflective of the intended clinical use for this indication. Therefore, the CHMP considered that the treatment indication is not appropriate and should be removed.
- The CHMP also considered the lack of evidence from clinical studies in the use of these products for the prevention of pneumonia, a severe infection, and therefore was of the view that it should not be recommended.
- The CHMP considered that the safety data reviewed was in accordance with the known profile of the products.
- Therefore, the CHMP considered that the benefit-risk balance of bacterial lysates based medicinal products for use in respiratory conditions is unchanged in the prophylaxis setting provided the efficacy and safety of the products are further characterised through the conduct of appropriate phase IV double-blind, multicentre, RCT(s).

In view of the above, the Committee considers that the benefit-risk balance of bacterial lysates based medicinal products for use in respiratory conditions remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for bacterial lysates based medicinal products for use in respiratory conditions.