Research Article

Can Asthma be Controlled in Children without using Chemical Drugs? Preliminary Clinical Results with a Protective & Nasal Surface Cleaning Polymeric Osmotic Film

Remi Shrivastava[1†], Megha Vijay[2], Sayali Sadgune[3], Ankit Samadhiya[4]

ABSTRACT

Background: Asthma is a multifactorial, immunological disease, having a complex physiopathology involving the contact between asthma triggering factors and the nasal mucosa, nasal mucosa damage, release of disease-specific TSLP and other proinflammatory cytokines such as IL-5, 6, 25, 33, responsible for persistent Upper Respiratory Tract (URT) inflammation. An effective treatment must prevent asthma trigger and should be multitarget, but all current treatments are either chemicals, mono-target, or symptomatic and are not adapted for long-term use in children. We evaluated the efficacy and safety of an osmotically active, stable, non-irritant, and totally safe nasal surface film to simultaneously protect, clean, remove inflammatory cytokines, reduce nasal mucosa inflammation and reconstitute the natural defensive barrier of the nasal mucosa, to minimize the intensity, frequency, and duration of asthma exacerbations as a preventive measure.

Methods: We conceived a glycerol-based, polymeric, stable, osmotic solution for topical application on the nasal surface. The filmogen solution was filled in 15-ml nasal sprays (Asmidine®, 125 µl/spray t.i.d.) and its preventive efficacy and clinical safety wer e com pared to Salbutamol (100 µg/dose, 1-2 oral puffs, t.i.d.) during an 84-day clinical trial including 12 children in Asmidine group and 11 in Salbutamol group, aged 8 years-18 years old, conducted as per GINA recommendations. The trial was approved by the Ethics Committee and was registered under n°: CTRI/2021/06/034142 (http://ctri.nic.in) by Mudra Clincare, Mumbai, India.

Findings: Both test products markedly increased Peak Expiratory Flow rate (PEFR) and forced Expiratory volume (FEV1), controlled Bronchial Asthma (BA), improved quality of life of children, reduced the need for SABA and minimized the frequency of asthma exacerbations, without any drug-related adverse effects. The efficacy of Asmidine® was progressive and only slightly lower compared to Salbutamol.

Conclusion: Asmidine®, registered as a new generation of asthma prevention medical device in Europe, is the 1st multitarget, safe, and effective asthma treatment alternative to chemical drugs.

Keywords: Asthma, Children, Prevention, Polymers, Safe, Medical device

Abbreviations: **GINA:** Global Initiative for Asthma, **PEFR:** Peak Expiratory Flow Rate, **FEV:** Forced Expiratory Volume, **BD:** Bronchodilator, **BA:** Bronchial Asthma, **ACQ-5:** Asthma Control Questionnaire, **NM:** Nasal Mucosa, **TSLP:** Thymic Stromal Lymphopoietin, **IL:** Interleukin, **SABA:** Short-Acting Beta2 Agonists, **AE:** Adverse Event, **SAE:** Severe Adverse Event

Introduction

Among children pathologies, asthma is the most common chronic and uncurable disease affecting nearly 300 million children worldwide in 2019 and is expected to reach 400 million by 2025 [1]. The World Health Organization estimated that nearly 250,000 people, mostly children, die prematurely each year from asthma [2]. The exact aetiology of asthma trigger is not known, as multiple genetic and environmental factors such as smoke, diet, medications, pollutants in vehicle exhaust fumes, antibiotics, allergens, animal hair, mites, mold, fungus, and pollens, are associated with asthma development Recent findings clearly show that traffic-related air pollution and immune disfunction are the main causes of asthma in urban areas of developing countries [3, 4]. Paediatric asthma is often under-diagnosed

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[1]Research scientist, Department of neurology, University of Clermont Auvergne, Clermont, France

[2]Mudra Clincare, Navi Mumbai, India

[3]Head Med affairs, BAMS, Mudra Clincare, Navi Mumbai, India

[4]Medical Device research scientist, Polytrap Pharma, Indore, India

[†]Author for correspondence: Dr. Rémi Shrivastava, Research scientist, Department of neurology, University of Clermont Auvergne, Clermont, France, E-mail: remi.s@naturveda.fr

and under-treated, particularly in low- and middleincome countries. Children with under-treated asthma suffer from respiratory difficulty, sleep disturbance, tiredness during the day, and poor concentration, thus seriously affecting their school performance, social life, and financial condition of the family and wider community. Asthma exacerbations with severe respiratory symptoms may need emergency care and hospitalisation for treatment and monitoring. In the most severe cases, asthma can lead to death [5]. Asthma involves a highly complex immune modulation process on the airway epithelium. Recent studies demonstrated that the airway epithelium produces cytokines in response to asthma triggering antigens and pollutants. These epithelial-derived cytokines include Thymic Stromal Lymphopoietin (TSLP), IL-25, and IL-33 activating type 2 Innate Lymphoid Cells (ILC2), which generate Th2 cytokines, such as IL-5 and IL-13 and induce Th2 induced respiratory tract inflammation [6]. Additionally, there is evidence to suggest that IL-33 may directly affect mast cell activation, airway smooth muscle migration, inflammation and release of multiple inflammatory mediators from eosinophils, T cells, macrophages, and neutrophils which cause damage to the airway, bronchoconstriction, stimulation of epithelial cell inflammatory pathways, and remodelling of URT tissue [7, 8].

Being a multifactorial disease, there is no specific treatment to cure asthma and all treatment strategies are therefore directed to manage, control, prevent, and provide symptomatic relief, particularly in case of acute attacks. Current treatment of asthma in children, depending on the frequency and the persistency of attacks, is either a symptom reliever or a preventive medication. However, all these drugs are chemicals and cannot be recommended for long-term us in children [9]. Symptomatic treatments include short-acting beta-2 agonists like salbutamol (Ventolin®, Asmol®) and terbutaline (Bricanyl®) to help relax the narrowed airway passages and make it easier for air to get through. In case of strong asthma attacks, the child might be given corticosteroids (prednisolone) to reduce inflammation and swelling in the airway passages [10]. The same treatments can also be given daily, in lower doses, to prevent asthma attacks. Other preventive medications include inhaled corticosteroids like beclomethasone, budesonide, fluticasone and ciclesonide; oral corticosteroid tablets or mixtures (prednisolone), sodium cromoglycate inhaler or montelukast tablets as alternatives to corticosteroids; or combination inhalers, which combine inhaled corticosteroid and long-acting beta-2 agonists like fluticasone and salmeterol, budesonide and formoterol, flucticasone and vilanterol [11, 12]. New biological drugs which minimize the activity of one or two cytokines like omalizumab and mepolizumab are given by injection every 2 weeks-4 weeks and are used for severe asthma, not controlled by other preventers [13]. Children in cases as such, need to take preventative medications every day.

All these chemical or biological treatments, acting on one of the cellular physiological functions, cannot be totally safe as they also affect other cellular parameters, even if the pharmaceutical industries claim reasonable safety. Being a disease that severely affects quality of life, patients just need a device or drug, which is safe, and which can minimize the frequency, intensity, and/or the duration of attacks and help them reduce the use of other toxic chemical or biological drugs [14]. The best hypothetical approach consists in protecting the Nasal Mucosa (NM) against asthma triggering factors; and /or simultaneously reducing the concentration of immune cells, TSLP, and other pro-inflammatory cytokines from the NM surface to minimize NM inflammation and to provide ideal conditions for quick NM natural repair [15, 16]. Such a multitarget approach should automatically lower intensity, frequency, duration of asthma attacks, and in turn the need for chemical treatments to improve quality of life of patients. As no single chemical entity can fulfill these multiple yet basic requirements, we envisaged conceiving an osmotically active liquid which can form a protective, resistant, non-irritant, and absorbent film over the nasal mucosa surface.

Methods

■ Conception of an osmotic and stable nasal film

The technology used to conceive the osmotic glycerol based, contaminant trapping, stable, nonirritant polymeric film has already been described by Shrivastava et al. [17, 18]. The polymeric film was presented as an osmotic liquid capable of forming a stable (4h-6h), absorbent film when sprayed on the nasal surface as described by Shrivastava et al. [19]. When applied on the NM, this polymeric film attracts hypotonic liquid from the NM tissue, thereby detaching and draining all NM surface

contaminants towards the absorbent film where they can be trapped. The aim was to protect the NM from environmental asthma triggers and to keep the NM durably clean.

■ Clinical study design

Type of study performed: An 84-day, open-label, randomized, comparative study to evaluate preventive efficacy and safety of the test product (Asmidine®) nasal spray versus Salbutamol metered-dose inhaler, in patients with partially controlled asthma. The first patient was recruited end of June and the study ended mid-December 2021.

■ Clinical trial oversight

The study was sponsored by VITROBIO France and was performed by MUDRA CLINCARE, Koparkhairane, Navi Mumbai-400709, India as per the Global Initiative for Asthma (GINA) committee recommendations for such studies. The study included children as well as adults, but the results were presented separately for each population. The protocol was approved by relevant ethics committees (Altezza Institutional Ethics Committee, Shree Ashirwad Hospital, Dombivli, Maharashtra, India) and institutional review boards. The trial was registered under n°: CTRI/2021/06/034142 (http://ctri.nic.in) on the 10th of June 2021. The authors vouch for the conduct of the trial, adherence to the protocol, the accuracy and completeness of the data, and reporting of adverse events. The trial complied with the International Conference on Harmonization Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and relevant national and local regulations. At the time of screening, the children's parents signed written informed consent forms. The sponsor provided the trial medication and supplied relevant investigation product information.

■ Study population

Being a pilot clinical trial, the aim was to include minimum 12 boys and/or girls between the ages of 7 years-18 years in each group.

■ Inclusion and exclusion criteria

At the time of recruitment, patients were examined physically, medical history was checked and vital parameters such as blood pressure, heart rate, respiratory rate, and body temperature were measured. The main inclusion criteria were patients aged between 07 years and 18 years; diagnosed with persistent and insufficiently controlled Bronchial Asthma (BA) at least 6 months before the screening visit; having above 2 asthma symptoms weekly with nocturnal awakening; requiring rescue medication more than 2 times a week, having activity restriction due to Bronchial Asthma (BA), having mean Asthma Control Questionnaire-5 (ACQ-5) test index in a range of ≥ 0.75 and<1.5; Forced Expiratory Volume in 1 second (FEV1) before the use of bronchodilators>60% and not under low-dose Inhaled Glucocorticosteroids (iGCS) therapy for minimum 2 months before screening. The main exclusion criteria were patients with the need of maintenance therapy of BA; contraindications to iGCS, hypersensitivity to terbutaline, salbutamol or any components of the study product; diagnosis of Chronic Obstructive Pulmonary Disease (COPD); recording unexpected deterioration of BA symptoms; or having pulmonary tuberculosis.

■ Randomization

After screening, patients meeting all the inclusion criteria and none of the exclusion criteria were randomized into 2 arms using SAS Version 9.1.3, following a randomization schedule. Block Randomization methodology was employed for generating the list. Within the block, the treatments were distributed in the ratio of 1:1. Each patient received a unique screening identification number, randomization code, enrollment identification number, and a personal diary for daily recordings.

■ Product Presentation and application

The nasal osmotic filmogen solution, termed Asmidine® Spray was supplied by VITROBIO SAS, France (ISO 13485 certified) in 15-ml plastic containers (± 125 sprays; 120 µl/spray) and contained a slightly viscous, brownish liquid. Asmidine® was used by applying 2-sprays in each nostril, t.i.d. for up to 84-days. Salbutamol, a short-acting β2 adrenergic receptor agonist bronchodilator, which relaxes airway smooth muscles and used as a preventive or symptomatic treatment was purchased from commercial sources (ASTHALIN inhaler from Cipla India Ltd., containing salbutamol 100 mcg/dose, 200 metered doses/inhaler) and was used by inhaling 1 or 2 oral puffs, t.i.d. up to day 84 [20]. The choice of regimen and duration of therapy corresponds to the recommendations presented in the GINA 2018 and the Federal Clinical Guidelines for diagnosis and treatment of BA [21].

Parameters Recorded

Patients' health-related parameters were recorded at randomization visit 1 (week-1), visit 2 (week-4), visit 3 (week-8), and visit 4 (week-12). Parameters recorded were based on GINA recommendations for asthma clinical evaluation and included Peak Expiratory Flow Rate (PEFR), indicating the maximum flow rate (expressed in liters per minute L/min) generated during a forceful exhalation, starting from full inspiration. The Forced expiratory Volume in 1 second (FEV1), which measures the maximum amount of air the patient can forcefully exhale in one second, was recorded through spirometry. A reduction of FEV between 20%-40%, 40%-60%, or above 60% can indicate mild, moderate or severe pulmonary obstruction. In addition, all adverse events, were recorded, Bronchial Asthma (BA) control assessment was done by calculating Asthma Control 5-Questionnaire index (ACQ-5) to evaluate the number of patients achieving BA after 84-days of treatment in each group compared to the baseline data. The Quality of Life (QOL) parameters was assessed with SF-36 eight scale questionnaire based on Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH), on a 0-100 scale. Mean values were calculated; lower scores indicating higher disability. Other auxiliary parameters were physical and vital signs (heart rate, blood pressure, breathing rate, body temperature), hematological, blood biochemical, and urinalysis were controlled at each visit.

Study Endpoints

The long-term preventive efficacy of Asmidine® compared to Salbutamol was evaluated at visits 1, 2, 3, and 4 by comparing changes in mean PEFR, FEV1 values (FEV was also recorded 2h after 1st and last product administration), average weekly need for SABA (terbutaline preparation); and the number of patients with exacerbations at visits 2, 3, and 4. The changes of ACQ-5 index and Quality-of-Life SF-36 questionnaire at the end of the study were compared with starting baseline values. The number of patients reaching BA control (<0.75 index according to the ACQ-5 questionnaire) was measured at Visit 4. Safety Endpoints included total number of AEs (Adverse Events) by severity and frequency, occurrence of AEs and SAEs (Severe Adverse Events) associated with the use of the study/reference product, the number of patients with at least one registered AE, and the proportion of patients who discontinued treatment due to AE in each group.

■ Statistical analysis

For clinical parameters, a change in FEV1, (volume of air exhaled during the first second of forced exhalation) between visits 4 and 1 was used as a primary efficacy endpoint. Comparison of the parameters in two groups of patients was performed by calculating 95% confidence interval for the difference of μe and μs, where μe and μs are the mean change compared to the baseline values in the groups of patients receiving study and comparator products, respectively (μ corresponds to the difference between visits 4 and 1). The study product is considered noninferior to the reference product, if the lower limit of 95% confidence interval for the difference of μe and μs is greater than Δ = -0.037 ml. as per FDA guidelines for choosing a margin of noninferiority in asthma clinical studies. The statistical analyses were based on null hypothesis (H0) where treatment with the use of the study product is inferior or HA hypothesis where it is superior to the treatment with the reference product. The sample size for such a comparative study was calculated by a statistician.

Results

■ Demography

The trial demographic distribution is shown in consort diagram. Among the 25 children enrolled for screening, 2 failed the screening test and 23 were randomized into two groups. 12 children (5 boys and 7 girls) were allocated in the Asmidine® group and 11 children (7 boys and 4 girls) were allocated in the Salbutamol comparator group. There were no dropouts during the study period. Mean age was 12.17 (± 4.02) years in Asmidine® group and 12.18 (± 3.37) years in Salbutamol group.

Effect on Peak Expiratory Flow Rate (PEFR)

The PEFR is an indication of the capacity of the lungs to accommodate air which is reduced in asthmatic children and particularly with increasing age. Normal PEFR ranges between 300 L/min-400 L/min in age groups, lower in the young children between 7 years-12 years but comparable to adults from the age of 12 and above [22]. The

mean baseline PEFR values before treatment were nearly 30%-50% less than the normal values in both groups (between 191 L/min-195 L/min), lower in girls compared to boys. After the start of treatment, a strong and progressive increase in PEFR was observed in both groups but improvement was faster in salbutamol group, particularly after 4 weeks of treatment (Figure 1). After 4 weeks, 8 weeks, and 12 weeks of treatment in Asmidine® group, the mean PEFR was 246 (± 7.33), 317(± 16.58), and 346 (± 10.19) L/min showing mean improvement of nearly 28%, 65%, and 80% compared to baseline values. In Salbutamol group, mean PEFR was 255(± 11.28), 347(± 13.47), and 405(± 13.13) L/min. after 4, 8, and 12 weeks, reflecting a remarkable increase of 31%, 78%, and 108% compared to baseline values. Although, the mean PEFR reached normal levels in both groups after 8-12 weeks of treatment, improvement was faster with salbutamol treatment with statistically significant ($p<0.001$) difference v/s Asmidine® at week 8 week and 12 week.

Forced Expiratory Volume (FEV1)

FEV1 is the amount of air forced from the lungs by an individual in one second which is reduced in case of air-flow obstruction of respiratory tract in asthma patients. FEV varies considerably with the age and sex of children. FEV in girls is generally 10%-20% lower compared to boys of the same age but it depends on the body surface area. The mean scores of FEV1 were similar in both groups (mean 2.41 L ± 0.07 L) at the start of the study. After 4-weeks of regular treatment, mean FEV1 progressed by nearly 18% in Asmidine group (mean value 2.85 ± 0.05) while the increase was 19% in the salbutamol group (mean 2.87 ± 0.04), with statistically a significant increase v/s baseline in both groups. A mean FEV1 above 2.8 L in children between 7-18, can be considered without air-flow obstructions. At the end of week-8 and 12, the mean FEV1 was 3.01 (± 0.06) and 2.85 (± 0.07) in the Asmidine treated children v/s 2.96 (± 0.07) and 2.97 (± 0.04) in the salbutamol group (Figure 2). These results show that both treatments are rapid with respect to normalizing FEV in children within 4-weeks but once the minimal normal FEV is achieved, there is not much change over a period of 12 weeks of treatment. FEV1 was also recorded 2 h after the 1st (day 1) and last (day-84) product applications in both the groups to verify any instant pharmacological effect. At both time points, Asmidine® showed no effect at all indicating that Asmidine® is not an instant acting drug. On the contrary, in the Salbutamol group, the mean FEVs increased by nearly 16% on day-1 and by 4.6% on day-84 v/s values before treatment on the same day. The 2h post-treatment improved FEVs in Salbutamol group confirms this drug has an instant muscle relaxant mode of action. These results, coupled with PEFR (capacity of lungs to accommodate air), prove that both Salbutamol and Asmidine® remarkably improve lung respiratory parameters in asthma patients but Asmidine® cannot be used as an instant relief treatment during an asthma crisis.

Asthma Control Questionnaire (ACQ-5)

As per GINA recommendations, lung functions were scored employing a grouped questionnaire, representing 5-items, where a BA control score <0.75 indicates well-controlled asthma, and >1.5, poorly controlled asthma [23]. At the start of the study, the mean ACQ-5 score of Asmidine® group was 1.1 (± 0.18) compared to 0.9 (± 0.29; $p<0.001$) in the reference Salbutamol group. The mean baseline score of Salbutamol treated group (0.9 ± 0.29) progressed during the 1st 4-weeks up to 1.20 (± 0.28) ($p<0.001$ v/s baseline) and returned to the baseline mean (0.9 ± 0.22) at the end of week-8, indicating that salbutamol has no effect on BA control during the 1st 8-weeks. Thereafter, the BA control score decreased to 0.6 (± 0.19) at the end of week-12. In the Asmidine® group, there was no change up to day-28, a slight reduction (1.0 ± 0.14; NS) was observed at the end of week-8 and further up to 0.8 (± 0.17) at the end of week-12. The mean reduction after 12-weeks of treatment vs baseline was nearly 33% (0.9 to 0.6) in Salbutamol and 27% (1.1 to 0.8) in the Asmidine® group. This change is significant and shows that both products help control BA but a minimum treatment of 8-weeks is required to observe noticeable effects. Asmidine® acts progressively while salbutamol is slightly more active compared to Asmidine® at the end of week 12 ($p<0.05$ between 2-groups on day 84). The number of patients in each group having BA controlled at the start and at the end of the study are shown below (Table 1).All except 2/11 children in Salbutamol group had partially controlled BA (ACQ-5 score <0.75) at baseline but at the end of the study, asthma was controlled in all the patients. Although both

Table 1: Bronchial Asthma Control in patients at baseline and at the end of the treatment (day 84)

ACQ-5 index	Salbutamol (n=11)	Asmidine (n=12)
Patients with Partially-controlled asthma, baseline (day 1) 0.75-1.5	No. of patients 09 (81.8%)	No. of patients 12 (100.0%)
Patients with Well-controlled asthma, baseline (day 1) (<0.75)	No. of patients 02 (18.2%)	No. of patients 0 (0%)
Patients with Partially-controlled asthma, Visit 4 (day 84) (0.75-1.5)	No. of patients 03 (27.3%)	No. of patients 9 (75%)
Patients with Well-controlled asthma, Visit 4 (day 84) (<0.75)	No. of patients 08 (72.7%)	No. of patients 3 (25%)

*In the Asmidine group 33.3% of patients (4 nos.) has a score of 0.8, and zero patient has a score of greater than 1 by the end of the treatment.

Table 2: QOL Scales/Parameters MEAN (± SD) score at baseline and at the end of the treatment (day 84) in Comparator and test product.

Mean values (SF-36 Scales)	Salbutamol (n=11)	Asmidine (n=12)	
Mean value, baseline (day 1)			
Physical functioning	50.5 (± 9.07)	49.6 (± 10.97)	
Role limitations due to physical health	77.3 (± 17.52)	77.1 (± 16.71)	
Role limitations due to emotional problems	72.7 (± 25.03)	55.6 (± 25.97)	
Energy/fatigue	45.5 (± 3.50)	45.4 (± 5.82)	
Emotional well-being	40.4 (± 3.78)	44.3 (± 5.77)	
Social functioning	39.8 (± 10.92)	44.8 (± 11.26)	
Pain	52.3 (± 11.09)	50.6 (± 13.62)	
General health	41.8 (± 4.62)	42.9 (± 5.42)	
Mean value, (day 84)			**Difference vs comparator**
Physical functioning	70.5 (± 8.50)	81.3 (± 8.01)	(-10.80)
Mean change from baseline	20.0 ± 0.57	31.7 ± 2.96	
Role limitations due to physical health	88.6 (± 17.19)	87.5 (± 13.06)	(1.14)
Mean change from baseline	11.3 ± 0.33	10.4 ± 3.65	
Role limitations due to emotional problems	84.9 (±17.39)	91.7 (± 15.06)	(-6.81)
Mean change from baseline	12.2 ± 7.64	36.1 ±10.91	
Energy/fatigue	56.4 (± 7.78)	55.4 (± 6.90)	(0.95)
Mean change from baseline	10.9 ± 4.28	10.0 ± 1.08	
Emotional well-being	54.2 (±10.02)	63.3 (± 7.0)	(-9.15)
Mean change from baseline	13.8 ± 6.42	19.0 ± 1.23	
Social functioning	53.4 (±15.90)	59.4 (± 12.07)	(-5.97)
Mean change from baseline	13.6 ± 4.98	14.6 ± 0.81	
Pain	69.8 (± 8.77)	62.5 (± 14.66)	(7.27)
Mean change from baseline	17.5 ± 2.32	11.9 ± 1.04	
General health	61.4 (± 12.67)	69.2 (±11.25)	(-7.8)
Mean change from baseline	19.6 ± 8.05	26.3 ± 5.83	

*Parameters are presented as mean ± SD. A Two-Way ANOVA followed by the Šídák's multiple comparisons test for comparison between the investigational group and comparator group (*p<0.05, p**<0.01, ***p<0.001). No significant difference was observed between the two groups, however a small but visible variance can be noticed in the results (MEAN±SD) at the end of the treatment (day 84).

treatments are remarkably active, week 12 results show that Salbutamol acts faster in controlling BA v/s Asmidine® and requires less duration to achieve BA control.

■ Quality of Life (QOL) assessment via SF-36 (Short Form Survey)

SF-36 questionnaire (Short Form Survey-36) is a non-specific questionnaire for the assessment of overall well-being and degree of satisfaction with the aspects of human activity in which 36 questions are grouped in 8 QOL parameters Higher scores indicate better QOL (Table 2) [21].

As shown in Table 2, both Asmidine® and salbutamol treatment for a period of 12 consec-tive weeks significantly improved the QOL of children. Compared to baseline, Asmidine® treatment improved physical functioning by 63.9% (p<0.001), role limitations due to physical health by 13.5%(NS), role limitations due to emotional problems by 64.9% (p<0.001), improved energy/less fatigue by 22.0% (p<0.001), emotional wellbeing by 42.9% (p<0.001), social functioning by 32.6% (p<0.006), reduction in pain sensation by 23.5% (p<0.05), and overall general health by 61.3% (p<0.001). Except for sensation of pain reduction and improved energy, the results of Asmidine® on 6/8 QOL life indicators were slightly or considerably better compared to Salbutamol.

These results, evaluated after 12-weeks of treatment, show that Asmidine® is nearly as good as salbutamol in improving the QOL of children in a long-term treatment.

■ Average weekly need for SABA (short-acting β-agonists, terbutaline preparation)

Only 1/12 child in Asmidine® group was administered 250 µg terbutaline on day 20 while no other treatments were required in the Salbutamol group indicating that both treatments are capable of controlling/preventing asthma and minimize the need for acute treatments.

■ Exacerbations

1 exacerbation was observed in Asmidine® group between Visit 1- Visit 2. A worsening or "flare up" of respiratory symptoms, known as an exacerbation in COPD, reflects both the effectiveness and safety of treatment. When compared to the Salbutamol group, only one patient in the Asmidine® group experienced an exacerbation between week 1 and week 4 of the study. These findings show that, after 4 weeks – 8 weeks of treatment, both treatments are well tolerated and help in reducing COPD exacerbations.

■ Adverse Events (AE)

In both treatment groups, no Serious Adverse Events (SAEs) were recorded and no patients in the clinical trial discontinued the study due to adverse events. 4 children in the Salbutamol group and 1 in the Asmidine® group experienced minor side effects. Occasional complaints in Asmidine® group included nasal irritation (1/12) while in the Salbutamol group, the 4 complaints concerned sensation of dizziness, stuffy nose, or nausea, during the study period. As the AEs were transient, disappeared rapidly, and were observed only in a few participants, they are not considered related to the treatment.

■ Other parameters

The participants in both groups underwent a battery of medical tests including blood chemical analysis, blood count, vital signs, and urinalysis but no significant change compared to baseline data, or between the groups, was recorded at the end of the study.

Figure 1 represents the PEFR, indicating the maximum air flow rate generated during a forceful exhalation, starting from full lung inflation, and was measured with a peak flow m eter f rom b aseline to day 84. The mean PEFR1 in total population with statistical difference (two-way A nova/Sidak; *p<0.05, ** p<0.01, and *** p<0.001) between the Salbutamol and Asmidine® group children at each endpoint compared to mean Baseline (BL) value.

Figure 2 represents the maximum amount of air expelled from the lungs within 1 second (FEV1) and was measured with a spirometer at each visit. Mean FEV1 in and total population with

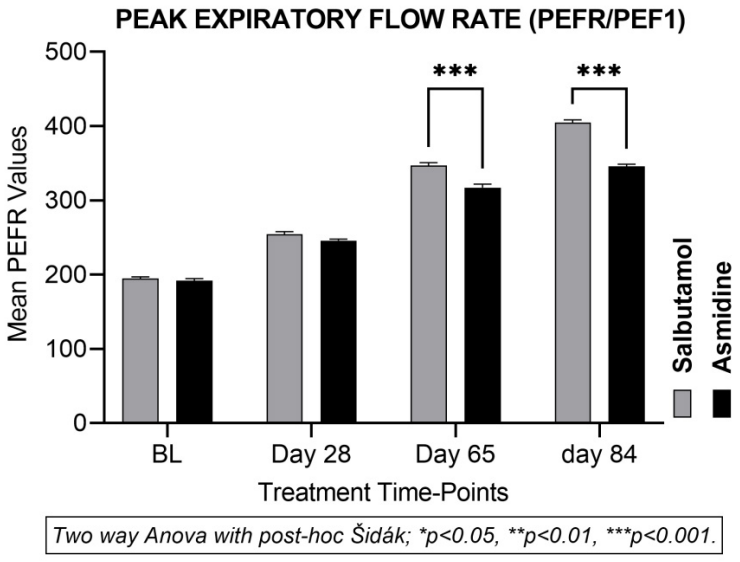

Figure 1: Peak Expiratory Flow Rate.

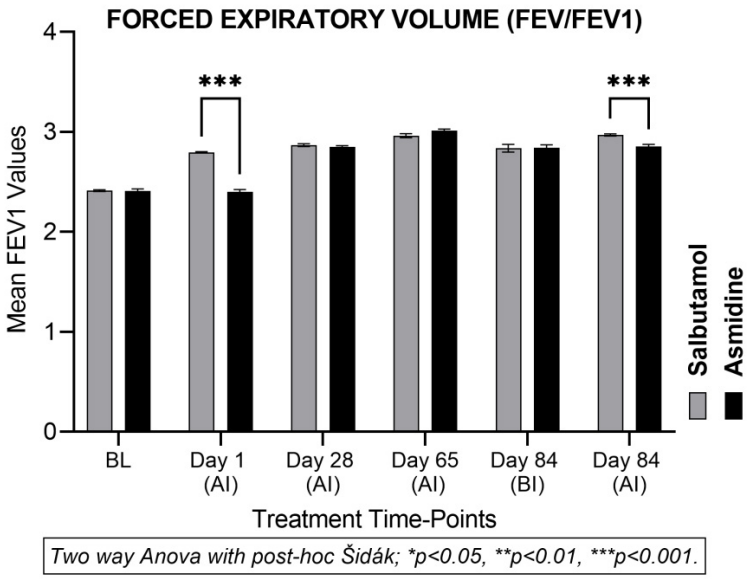

Figure 2: Forced Expiratory Volume (FEV).

Figure 3: Asthma Control Questionnaire.

statistical difference (two-way Anova/Sidak; *p<0.05, ** p<0.01, and *** p<0.001) between the Salbutamol and Asmidine® groups at each visit compared to mean Baseline (BL) value. BI stands for before product inhalation mean values, AI stands for after product inhalation mean values.

Figure 3 represents the lower ACQ mean scores indicate which better controlled asthma. The scores indicate, well controlled (ACQ≤0.75), partly controlled (0.75>ACQ≤1.5) or uncontrolled (ACQ>1.5) asthma. Statistical difference (two-way Anova/Sidak; *p<0.05, ** p<0.01, and *** p<0.001) between the Salbutamol and Asmidine groups at each endpoint compared to mean Baseline (BL) value.

Figure 4 represents the number of patients screened, allocated, lost to follow-up and analyzed.

Discussion

The asthma epidemic in children experienced by developed nations over the last 30 years is now

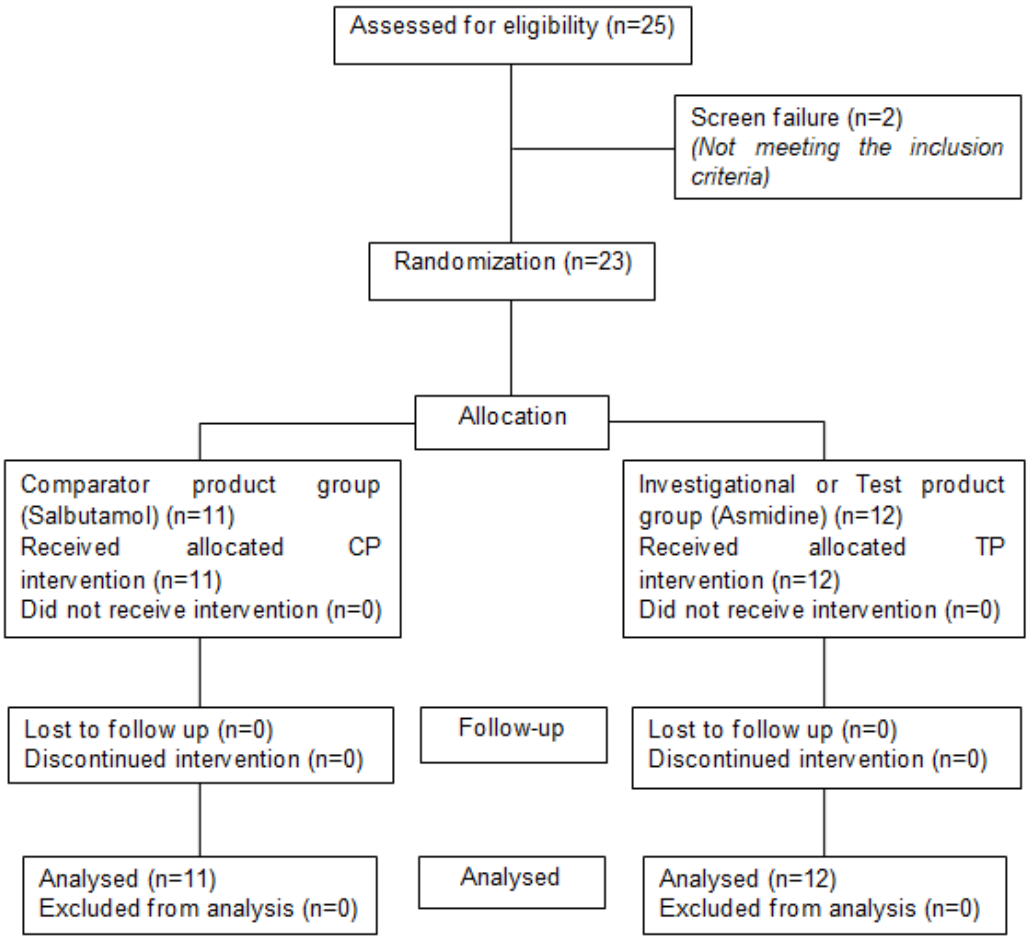

Figure 4: Consort Diagram.

seriously affecting children in developing nations and becoming one of the most common chronic diseases [24]. Most of these patients are based in urbanized cities and are exposed to increasing city pollutants. Numerous studies have shown that children living in environments near traffic areas have increased risk of asthma symptoms, asthma exacerbations, school absences, asthma hospitalizations as well as new-onset asthma [25].

The understanding of asthma physiopathology has dramatically evolved over the past 20 years, and it is now clear that asthma is not a single disease, but rather a multifactorial disease syndrome that can be caused by multiple biologic and immune mechanisms. It involves multiple biological proteins such as the lymphokines (IL-4, 5, 9, 13, 17) which increase the production of IgE and inflammatory cells but also the proinflammatory cytokines such as TSLP, IL-6, IL-1β, TNF-α, immune cell recruiting chemokines (CCL-2, 5, 11) and cellular remodelling growth factors such as GM-CSF, SCF, TGF-β, VEGF, and EGF. These mediators are produced in and on URT, leading to extensive presence of multiple inflammatory mediators and immune cells on the surface of the NM which continue maintaining widespread URT inflammation, cellular damage, rupture of nasal epithelial mucosa integrity, and persistent inflammatory cascade [6, 26, 27]. Severe and chronic URT inflammation leads to the narrowing of small airways in the lungs, excessive mucus production, cough, wheezing, shortness of breath and chest tightness [7]. It is understandable that such a complex pathology cannot be treated with one or two target oriented, chemical or biological drugs.

Currently, there are neither curative drugs nor even preventive treatments which can stop or even minimize the frequency, intensity, and/or the duration of asthma exacerbations. They are prevented, to some extent, only through regular use of bronchodilators, corticosteroids, or single protein targeted biologicals during the entire disease period [28]. Even if such treatments are

claimed to be relatively safe, their long-term regular use represents a considerable health risk, particularly for children [29]. Recently, several new asthma medications, known collectively as "biologics," have been approved for the treatment of moderate-to-severe asthma. Biologics are unique in that they target a specific antibody, molecule, or cell involved in asthma. Because of this, they are also known as "precision" or "personalized" therapy [30]. The biologics block one or hardly two asthma proteins but do not normalize other factors also involved in the disease. The key FDA approved biologics, companies, and their cytokine targets are: Cinqair (GSK-Teva, reslizumab, IL-5), Dupixent (dupilumab, IL-4, 13), Fasenra (AstraZeneca, benralizumab, IL-5), Nucala (GSK, mepolizumab, IgG1 kappa anti-IL-5), Tezspire (Amgen-AstraZenica, Tezepelumab, TSLP), and Xolair (Novartis, omalizumab, anti-IgE). The presence of multiple asthma specific proinflammatory cytokines on the NM which continue triggering inflammatory cascade as soon as children are exposed to any asthma activating factor, makes treatment of asthma impossible [30,31]. Only a multi-target treatment which can prevent or minimize further asthma trigger, inflammatory cascades, as well as simultaneously clean and repair the NM, can reduce asthma frequency, duration, and symptoms. For long-term use in children, such a medication should be totally safe, should act only on the NM surface, should not be absorbed in the body, and should not interfere with the cellular physiological functions. Asmidine® spray is a safe, osmotic, and absorbent topical barrier film which can protect the NM against incoming asthma triggering factors for 4h-6h. Being osmotic, the film continuously attracts hypotonic liquid from the NM thereby draining and detaching all free-floating protein molecules from the surface. Protecting and keeping the NM clean, reducing NM inflammatory proteins, and reestablishing NM integrity, just by using an osmotically active stable nasal film has shown to curb asthma symptoms and improve the patient's condition by reducing the frequency, intensity, and severity of asthma attacks.

Clinical trial results prove that Asmidine® spray is only slightly less effective compared to Salbutamol in improving PEFR, FEV1 and in controlling BA while the efficacy on reducing the need for SABA and corticosteroids, and the improvement in QOL, are comparable for both test products. The absence of any side effects or modifications in systemic parameters during the 12-week treatment period with Asmidine® proves that the polymeric osmotic film acts topically on the surface of the NM as a mechanical barrier /cleaner, without being absorbed and without any cellular interactions. Salbutamol inhalers are generally used as a lifesaving drug during asthma attacks as they relax airway muscles and open the airways to ease breathing for a few hours. In lower doses, the bronchodilator treatment can be associated with corticosteroids, longacting β-agonists, anticholinergics, or leukotriene receptor antagonists as a preventive therapy to minimize the occurrence, intensity, and/or frequency of asthma exacerbations [32]. These preventive therapeutic approaches are effective, but we should not forget that these drugs are chemicals, they are administered daily for years and years, the URT of children is fragile, these chemicals are absorbed in the body, and their long-term use side-effects are not totally elucidated. The basic question remains: Can long-term daily exposure of such drugs to children be considered safe? In the absence of any alternative, these questions were not raised but the results of the new polymeric osmotic filmogen technology presented in this study prove that keeping the NM clean and healthy may offer an excellent means of reducing systemic concentrations of pathogens and inflammatory proteins which are often released on the most vascularized and fragile organ in our body, the NM. Highly encouraging clinical results have already been observed for the treatment of viral infection [33], chemotherapy induced oral mucositis [34], and even Covid-19 [18]. Asmidine® being only slightly less effective than Salbutamol in improving PEFR, can easily be used as a non chemical safe asthma prevention replacement therapy to Salbutamol.

Conclusion

Continuous protection and cleaning of the nasal surface with a mechanically acting osmotic polymeric film (Asmidine®) is as effective as the use of Salbutamol in preventing and treating asthma in children. Asmidine® is a simple and safe but logical and scientific approach to minimize long-term use of unsafe chemical or biological drugs in children. In spite of using unsafe chemical and/or biological drugs for the treatment of asthma in children, Asmidine® nasal polymeric film may represent a great advance in the treatment of asthma in children.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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