

STUDY PROTOCOL Effect of Vaxoral® (OM-85) on frequency of upper respiratory tract infections and size of adenoid tissue in preschool children with adenoid hypertrophy	
Study Product(s)	Vaxoral® (OM-85)
Indication	Recurrent RTIs, adenoid hypertrophy
Sponsor	Dr Sami Ulus Maternity and Children Research and Training Hospital, Department of Pediatric Allergy and Immunology, Ankara, TURKEY
Anticipated Countries	Turkey
Introduction	<p>OM-85 significantly reduces RTIs in children. This effect was proved by many clinical studies and meta-analyses¹. A Cochrane meta-analysis first published in 2006 and updated recently (Del-Rio-Navarro 2012) showed that immunostimulants (IS) could reduce acute RTIs (ARTIs) by almost 39% when compared to placebo. Among the different IS, OM-85 showed the most robust evidence with 4 trials of “A quality” according to the Cochrane grading criteria. Pooling six OM-85 studies, the Cochrane review reported a mean number of ARTIs reduction by -1.20 [95% CI: -1.75, -0.66] and a percentage difference in ARTIs by -35.9% [95% CI: -49.46, -22.35] compared to placebo¹.</p> <p>Adenoid hypertrophy (AH) is one of the most important respiratory disease in preschool children². In normal conditions adenoid tissue enlarges up to 5 years and become smaller afterwards. But in some children who have recurrent URTIs, it keeps growing and this can be associated with complications². AH may cause recurrent respiratory infections and each infection contributes to enlargement of adenoid tissue thus promoting a vicious cycle. Additionally enlarged adenoids are known to be reservoir for microbes and cause of recurrent or long lasting RTIs³.</p> <p>AH is associated with chronic cough, recurrent and chronic</p>

sinusitis, recurrent tonsillitis, recurrent otitis media with effusion, recurrent other respiratory problems such as, nasal obstruction and sleep disturbances, sleep apneas²⁻³. Eventually, AH causes loss of appetite and growth delay; it is often associated with misuse or over use of antibiotics and often eventually requires surgery. It decreases quality of life both in children and parents and it represents a burden not only for families but also for HCS and society due to increased health cost⁴.

In one study which investigated the structural and immunological aspects of tonsils and adenoids of 105 children (54 males and 51 females, aged between 4 and 18 years) who were affected by chronic inflammatory hypertrophy of palatine tonsils and adenoids which had not responded to previous medical treatments and who underwent adenotonsillectomy because of recurrent inflammatory episodes with fever, it was demonstrated that deficit in the activation of the immune system could be represented by the small quantity of mRNAs for interleukin-2 (IL-2) and interleukin-4 (IL-4) detected in our population, suggesting a defective activation of Th1 and Th2 lymphocytes⁵.

Clinical research question: Can OM-85 reduce the recurrence of infections in children with AH by stimulating the immunological response of the host and therefore, as a consequence reduce the size of adenoid tissue in children with adenoid hypertrophy?

Can this prevent further complications as surgery need?

References:

1. Del-Rio-Navarro BE et al. Immunostimulants for preventing respiratory tract infection in children (Review) Evid.-Based Child Health (A Cochrane Review Journal).2012;7(2): 629–717.
2. Zautner AE. Adenotonsillar disease. Recent Pat Inflamm Allergy Drug Discov. 2012 May;6 (2):121-9.
3. Battistini A, Siepe F, Marvasi R. The tonsils and adenoids as a site of infection and the cause of obstruction. Pediatr Med Chir. 1998 Jul-Aug; 20(4):237-47.

	<p>4. Ericsson E, Lundeberg I, Hulcrantz E. Child behavior and quality of life before and after tonsillotomy versus tonsillectomy. <i>Int J Pediatr Otorhinolaryngol</i>. 2009 Sep;73 (9):1254-62.</p> <p>5. Passali D, et al. Structural and immunological characteristics of chronically inflamed adenotonsillar tissue in childhood. <i>Clinical and Diagnostic Laboratory Immunology</i> 2004; 11 (6): 1154–1157</p>
Rationale	<p>OM-85 is an oral bacterial lysate of 21 different strains of 8 species and sub-species of the most common respiratory tract pathogens that has been administered in millions of children above 1 year of age. OM-85 stimulates the innate immune system by improving alveolar macrophage activity in the BAL fluid of patients with airway disease, increasing dendritic cells activation and increasing antibodies in the lung of patients with airway diseases. OM-85 stimulates Th1 immunity and inhibits Th2 immunity¹.</p> <p>Its clinical efficacy in reducing the rate of RRTIs in children is supported by several well-designed and conducted clinical studies and it has showed a good benefit risk profile, unchanged in nature and frequency over more than 30 years of clinical paediatric use.</p> <p>A recent meta-analysis by Schaad et al. 2010² of 8 double-blind placebo-controlled trials conducted in children aged 1-12 years affected by recurrent infective episodes (≥ 3 RTIs in 6 months) has shown that the administration of OM-85 significantly reduced the mean number of RTIs by 35% vs placebo and that a lower proportion of treated patients (26.2%) experienced RRTIs. This effect was more evident in patients with the highest number of infectious in the year prior to study entry².</p> <p>The majority of studies used a children posology of 1 daily dose (3.5mg) for 10 days repeated for 3 consecutive months followed by 3 months or 9 months follow-up. In one study 2 cycles (10 days/3 months) at a 6-months intervals were used.</p> <p>An effective and well tolerated prevention of RRTIs with OM-85 could result not only in a positive effect on children's quality of life</p>

	<p>but also in economic benefit for patients' families and societies as recently reported in a pharmacoeconomic study by Zaniolo et al. 2013³ and Ravasio et al. 2015⁴.</p> <p>Because OM-85 significantly reduces RTIs in children, it is expected to be able to reduce the adenoid tissue size as a consequence of fewer inflammatory RTIs.</p> <p>References:</p> <ol style="list-style-type: none"> 1. De Benedetto F, et al. Prevention of respiratory tract infections with bacterial lysate OM-85 Broncho-munal in children and adults: a state of the art. Multidiscip Respir Med. 2013 May 22;8(1):33 2. Schaad UB. OM-85 BV, an immunostimulant in pediatric recurrent respiratory tract infections: a systematic review. World J Pediatr 2010; 6(1): 5-12. 3. Zaniolo O et al. Costo/efficacia della prevenzione di infezioni alle prime vie aeree mediante un estratto batterico immunostimolante aspecifico (OM-85). Farmaeconomia e percorsi terapeutici 2013; 3(6):169-184 4. Ravasio R. Economic analysis of the immunostimulant OM-85 for the prevention of paediatric recurrent upper respiratory tract infections. Global & Regional Health Technology Assessment 2015; 0(0): 00-00. DOI: 10.5301/GRHTA.5000200.
Objectives	<p>Primary Objective:</p> <ul style="list-style-type: none"> • Reduction of number of RTIs within 12 months <p>Secondary Objective(s):</p> <ul style="list-style-type: none"> • Reduction in duration of RTIs • Reduction of antibiotic use • Reduction of absenteeism (missed school days or missed days of work for parents) • Adenoid and tonsil health survey

	<p>(described in appendix 1)</p> <ul style="list-style-type: none"> • Reduction of the size of adenoid tissue (described in appendix 3) • Reduction of surgery need
Design, incl. Treatment	<p>This is a randomised, double-blind, placebo-controlled, parallel group, phase IV study.</p> <p>First group will receive OM-85 (10-10-10 standard treatment regimen)</p> <p>Second group will receive matching placebo at the same posology (10-10-10).</p> <p>A second cure of treatment will be given 6 months after inclusion.</p> <p>Patients will be recruited from 01 September 2017 to 01 March 2018. The trial will begin in September 2017 and will be completed in March 2019.</p> <p>By this way every patient will be studied over all seasons (1 year study).</p>
Inclusion Criteria	<ul style="list-style-type: none"> • Children (age: 2-6 years) • Who experienced recurrent RTIs (at least 3 episodes in 6 months before the inclusion) • Who have symptoms of AH (snoring; mouth breathing awake; mouth breathing asleep; nasal congestion; hyponasal voice; chronic nasal discharge; daytime drowsiness, or hyperactivity; restless sleep; sleep apnoea <15 sec; night cough; and poor oral intake/weight loss) based on the symptoms score questionnaire (described in appendix 1).
Exclusion Criteria	<ul style="list-style-type: none"> • Atopy • Gastroesophageal reflux • Immune deficiency • Asthma or allergic rhinitis • Premature delivery • Anatomic alterations of the respiratory tract; chronic respiratory

	<p>diseases (tuberculosis and cystic fibrosis); autoimmune disease; liver</p> <ul style="list-style-type: none"> • Kidney failure; malnutrition; cancer • Treatment with inhaled or systemic corticosteroids within the previous month • Treatment with immunosuppressants, immunostimulants, gamma globulins, or anticonvulsive drugs within the previous 6 months.
Endpoints	<p>Primary Endpoint: Cumulative number of RTIs over the 12 months.</p> <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Duration in days of RTIs • Antibiotic use (n. of cycles and days) • Missed school/work days • Adenoid and tonsil survey (described in appendix 1 of the original protocol) • Size of adenoid tissue over the 12 months according to radiographic and flexible nasopharyngoscopic evaluation (described in appendix 3 of original protocol). • Surgery need • AEs
Procedures	<p>Patients will be recruited from 01 September 2017 to 01 March 2018. The trial will begin in 01 September 2017 and will be completed 01 March 2019.</p> <p>Children with the ages of 2-6 years who have recurrent RTIs and AH will be evaluated for the eligibility for the study. When eligible for the study, children's all demographic characteristics will be recorded (Table 1). Eligible children will be evaluated by ear-nose-throat (ENT) specialist and flexible laryngoscopy and radiographic evaluation of adenoid size will be performed in order to measure the adenoid size. All children will be evaluated by an allergy specialist. Complete blood count, serum IgG, IgA, IgE, IgM will be measured.</p>

	<p>Skin prick test will be performed with common allergens.</p> <p>All children will be randomized into two study arms (active treatment and placebo). OM-85 3.5 mg capsule or placebo will be given according to the standard treatment schedule (10-10-10) for the three consecutive months. All patients will receive 2 cures of treatment at the beginning and 6 Months after inclusion in the study. Every patients will be followed-up for 12 months.</p> <p>Patients (and care giver/parents) will be given a symptom score form (Table 2) in order to record all nasal symptoms, signs and duration of RTIs, antibiotic use, days of absenteeism from school and from work for family members, monthly.</p> <p>All patients will be asked to come to the clinic when they have symptoms of RTI in order to diagnose the type of RTIs. Then they will be asked to complete the infection form during the acute RTIs (Table 3).</p> <p>Every 3 months they will fill in the Tonsil and Adenoid Health Status Survey (Table 4).</p> <p>Every 3 months patients will be asked to come to the clinic and all their records will be collected and they will be evaluated by the ENT specialist for the adenoid tissue size. All these parameters will be recorded in specific forms by the investigator (Table 5).</p> <p>Patients will be allowed to use nasal corticosteroids, antihistaminic drugs and flu vaccine during the study period and all these study medications will be recorded.</p> <p>At the end of the study (12 months), immunoglobulin levels will be measured to compare them with basal level.</p>
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Sample Size	<p>A total of 68 patients will be randomized in the study in a 1:1 ratio to Active or Placebo groups.</p> <p>Active group: 34 patients</p> <p>Placebo group: 34 patients</p>
N° Sites	<p>Number of study centers: 1</p> <p>Study center: Dr Sami Ulus Maternity and Children Research and Training Hospital, Department of Pediatric Allergy and Immunology, Ankara, TURKEY.</p> <p>Study Coordinator and Principal Investigator: Serap Ozmen M.D. Associate Prof. of Pediatrics and Pediatric Allergy, Training staff on Pediatric Allergy</p> <p>Other Investigators: Ilknur Bostanci M.D. Professor of Pediatrics & Subspecialist on Pediatric Allergy and Pediatric Pulmonology Chief of Pediatric Allergy and Immunology Department Vedat Tas M.D. Otolaryngologist Emin Cakmakci M.D. Radiologist</p>
Statistical Methods	<p>Statistical method:</p> <p>All analyses will performed with a commercially available software program (SPSS Statistical Software, version 11.5; SPSS, Inc, Chicago,Ill).</p> <p>The Shapiro-Wilks test will use to evaluate normality of the distributions collected. When variables were normally distributed, they were expressed as means (SDs); otherwise, they will express as medians and interquartile ranges (25th-75th percentiles). The χ^2 test will use for categorical variables and expressed as observation counts (in percentages). An ANOVA (or Mann-Whitney U depending on the normality of data) statistics will be used to compare means between both treatment groups for continuous variables. Bonferroni multiple comparison test will use to compared paired intervals (0-3, 0-6 months). All P values are 2-tailed; a P</p>

	<p>value of less than .05 are considered statistically significant.</p> <p>Sample Size:</p> <p>In one study OM-85 group showed 3 less RTIs compared with placebo over 12 months period. A sample size of 54 randomized patients (27 per group) will provide at least 80% power to detect a mean difference of at least 2.0 RTIs between the two groups assuming a SD of 2.55 and assuming a drop-rate of 20% after 6 months, total of 68 patients (34 per group) will recruit to the study.¹</p> <p>Reference:</p> <p>1. María Dolores Gutiérrez-Tarango and Arturo Berber. Safety and Efficacy of Two Courses of OM-85 BV in the Prevention of Respiratory Tract Infections in Children During 12 Months. CHEST 2001; 119:1742–1748</p>
Planned Timelines	<p>Planned date first patient consented/enrolled/observed: 01 September 2017</p> <p>Planned date last patient consented/ enrolled/ observed: 01 March 2018</p> <p>Planned date last patient last observation/ treatment: 01 March 2019</p> <p>Planned date CSR (Clinical study report) available: June 2019</p>

1. Visit	2. Visit	3. Visit	4. Visit	5. Visit	6. Visit
Randomization of the patients	After randomization treatment plan (OM-85 capsules or placebo given in the first 10 days of each month for 3 months)	Control at the end of 3rd month of treatment (20 days after the last medicine/drug or placebo)	Control after 3 months of last drug or placebo intake and Given the product by the previous randomization again for 3 months	At the end of the second 3-month treatment (20 days after the last drug)	Control after 3 months of the last drug or placebo intake (20 days after the last medicine/drug or placebo)
<ul style="list-style-type: none"> Patients will be assessed for type of respiratory infection and additional treatment by researchers (pediatric allergy specialists and/or ENT specialists) in the Pediatric Allergy and Immunology outpatient clinic when symptoms of respiratory tract infection is present. 					

- Parents will be asked to fill in the relevant form [Symptom Score Form] during this acute respiratory tract infection.
- Every 3 months, parents will be filled.QoLQ "Tonsil and Adenoid Health Status Survey".

Appendix 1. Study Forms

Table 1. Demographic charecteristics

PATIENT FOLLOW-UP FORM	
Date	
Patient Number	
Treatment group (Randomisation code)	
Name Surname	
Birth date	
Gender	
Smoking at home	
Family history of asthma	
Family history of atopy	
DPT	
IgG	
IgA	
IgE	
IgM	
FIRST VISIT	
RTIs in previous 12 months	
RTIs in previous 6 months	
Number of hospitalisation in previous 12 months	
Total days of hospitalisation in previous 12 months	
Total days of absenteisim from school	
Total days of absenteisim from work for mother	
Total days of absenteisim from work for father	
Antibiotic use in previous 12 months	
<ul style="list-style-type: none"> Number of box 	
<ul style="list-style-type: none"> Total number of days 	
Symptome score	

QoLQ (Score)	
Adenoid size	
<ul style="list-style-type: none"> Radiological (AC/SP ratio) 	
<ul style="list-style-type: none"> Nasopharyngoscope (perceived percent obstruction of the choana) 	

Table 2. Symptomes score (will be completed for each month)

Symptomes	none (0 point)	rarely (1 point)	frequently (2 points),	constantly (3 points)
Snoring				
mouth breathing awake				
mouth breathing asleep				
nasal congestion				
hyponasal voice				
chronic nasal discharge				
daytime drowsiness, or hyperactivitiy				
restless sleep				
sleep apnea <15 sec				
night cough				
poor oral intake/weight loss				

Scores from eleven symptoms were added together to provide a total symptom score of 33.

1- Sclafani AP, Ginsburg J, Shah MK, Dolitsky JN. Treatment of symptomatic chronic adenotonsillar hypertrophy with amoxicillin/ clavulanate potassium: short and long-term results. *Pediatrics* 1998; 101: 675-81.

2- Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclamethasone. *Pediatrics* 1995; 95:355-64.

Table 3. Infection form (will be completed for each infection)

Type of RTI	
Duration of RTI	
Antibiotic consumption (days)	
Days of absenteeism from school	
Days of absenteeism from work for family members	

Table 4. Tonsil and Adenoid Health Status Survey (It will be completed by the parents in every 3 months)

TONSIL AND ADENOID SURVEY

We are conducting a study on children with tonsil or adenoid problems, and we are interested in the type of health problems that your child is having related to his (her) tonsils and adenoids. There are no correct or incorrect answers, and your opinion is most important to us. The survey is completely voluntary and will take about 3 minutes to complete.

Please answer these questions remembering the **past 6 months** for your child. The questions relate to the problems many children have related to their tonsils and adenoids. If a certain question is not a problem for your child, please circle "0" (not a problem) for that question. Please do not skip questions or leave any questions unanswered.

Over the past 6 months, how much of a problem were the following conditions for your child?

Please circle the most correct response

	<i>Not a problem</i>	<i>very mild problem</i>	<i>moderate problem</i>	<i>fairly bad problem</i>	<i>severe problem</i>	
1. Snoring loudly during sleep	0	1	2	3	4	1
2. Strep throat infections	0	1	2	3	4	2
3. Many <u>trips</u> to a doctor's office	0	1	2	3	4	3
4. Taking antibiotics for more than <u>3 weeks straight</u>	0	1	2	3	4	4
5. Taking antibiotics <u>over and over</u> for less than 2 weeks at a time	0	1	2	3	4	5
6. Many <u>calls</u> to a doctor's office	0	1	2	3	4	6
7. Irregular or stopped breathing, also known as apnea, during sleep	0	1	2	3	4	7
8. Repeated short-term (or acute) infections of the tonsils that last less than 2 weeks	0	1	2	3	4	8
9. Constant, or chronic, infection of the tonsils that last more than 2 weeks	0	1	2	3	4	9
10. The cost of medical care and prescriptions	0	1	2	3	4	10
11. Breathing through the mouth during the day	0	1	2	3	4	11
12. Your child not growing or gaining weight as expected	0	1	2	3	4	12
13. Noisy breathing during the day	0	1	2	3	4	13
14. Problems with poor appetite or poor eating habits	0	1	2	3	4	14
15. Behavior problems at home or at school, or poor school grades or reports	0	1	2	3	4	15

Table 5. Follow-up form

Visit (3-6-9-12 months)	Date:					
Number of RTIs in previous 3 months:						
• Type	AOM	AS	AT	AN	AC	P

• Number						
• Duration (days)						
Antibiotic use in previous 3 months						
• Type						
• Number (box)						
• Duration (days)						
Hospitalisation:						
• Number						
• Duration (days)						
Symptome score						
QoLQ (Score)						
Adenoid size						
• Radiological (AC/SP ratio)						
• Nasopharyngoscope (perceived percent obstruction of the choana)						

Appendix 2. Definition of infections:

Acute nasopharyngitis (Common cold); was defined when nasal stuffiness or drainage, sore or scratchy throat, sneezing, hoarseness, cough, with or without fever and headache were present which resolved in 7-10 days.

Simasek M, Blandino DA. Treatment of the common cold. Am Fam Physician 2007;75: 515-20, 522.

Sinusitis; was defined when persistent symptoms of URTI (rhinoviral illness) were present without improvement after 10 days or a worsening of symptoms after 5 to 7 days with purulent nasal discharge, nasal congestion, postnasal drip, cough, and continued unwell state with or without fever, irritability, lethargy and facial pain

American Academy of Pediatrics Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: Management of sinusitis. Pediatrics 2001;108:798.

Acute otitis; was defined when acute onset of earache with erythema and limited mobility of the tympanic membrane determined by pneumatic otoscopy was present.

Tonsillitis; was defined when inflammation of one or both tonsils associated with a catarrhal exudate over the tonsil or the discharge of caseous or suppurative material from the tonsillar crypts was present

Viral croup; was defined when hoarseness, stridor and the characteristic “croupy” or barking cough developed after a viral prodrom by 12 to 72 hours of low-grade fever and coryza and resolved within one week.

Knutson D, Aring A. Viral Croup. Am Fam Physician 2004;69:535-40,541-2.

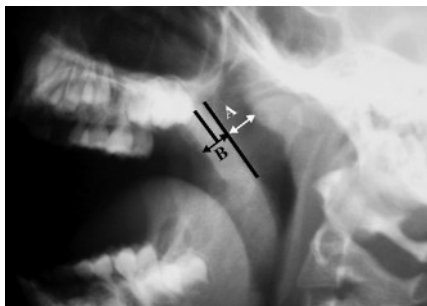
Pneumonia; was defined when fever, cyanosis, and more than one of the following signs of respiratory distress: tachypnea, cough, nasal flaring, retractions, rales, and decreased breath sounds were present with abnormal chest X-ray. (5,12,13). Pneumonia was diagnosed when tachypnea occurred in a patient younger than two years with a temperature higher than 38°C temperature. Children without fever or symptoms of respiratory distress didn't have the diagnosis of pneumonia.

Ostapchuk M, Roberts Dm, Haddy R. Community-Acquired Pneumonia in Infants and Children. Am Fam Physician 2004;70: 899-908.

Respiratory infections were also considered as mild or severe according to validated published criteria. Mild ARTIs involved the acute [nasopharyngitis](#) (common cold), tonsillitis or viral croup. Severe ARTIs involved the sinusitis, acute otitis or pneumoniae. Antibiotics were prescribed in the case of tonsillitis, otitis, sinusitis or lower ARTI.

Bardin PG, Fraenkel DJ, Sanderson G, Dorward M, Lau LCK, Johnston SL et al. Amplified rhinovirus colds in atopic subjects. Clin Exp Allergy 1994;24: 457-464.

Appendix 3. Radiographic evaluation of adenoid size:



Radiographic evaluation of adenoid size by the method of Cohen and Konak (1). Thickness (mm) of “Airway column” (A) and “Soft palate” (B) is measured and A/B ratio is calculated in order to evaluate nasopharyngeal airway patency.

Lateral neck radiographs will taken and interpreted by the method of Cohen and Konak by a blinded radiologis (1). According to this method, the thickness of the soft palate (SP) in its superior anterior part and the airway column (AC) immediately posterior to it will measured and AC/SP ratio was calculated. The measurement will done about 1 cm below the upper end of the soft palate in children > 3 years of age and half a centimetre in younger children. A radiographic example of this method is demonstrated in Figure 1.

Degree of obstruction was graded as follows:

AC/SP ≥ 1 (grade 0 or no obstruction),

AC/SP= 0.50-0.99 (grade 1 or mild obstruction),
AC/SP= 0.01-0.49 (grade 2 or severe obstruction),
AC/SP= 0 (grade 3 or total obstruction).

Cohen D, Konak S. The evaluation of radiographs of the nasopharynx. Clin Otolaryngol 1985; 10: 73-8.

Flexible nasopharyngoscope:

Topical anesthesia will use in the form of a mixture of lidocaine/ neosynephrine spray that will applied by pressurized nozzle prior to endoscopic examination. The patient will be seated upright in the examination chair without restraint during the exam. A standard 4.0 mm flexible nasopharyngoscope with attached fiberoptic light will be used to perform the nasopharyngoscopy. The data will be recorded as a perceived percent obstruction of the choana by the adenoid pad, as seen through the endoscope.

Lertsburapa K, Schroeder JW, Sullivan c. Assessment of adenoid size: A comparison of lateral radiographic measurements, radiologist assessment, and nasal endoscopy/International Journal of Pediatric Otorhinolaryngology 74 (2010) 1281–1285

Version 2, Date: 03. 23. 2017

Informed Consent Form

We invite you to the study, **“Effect of Vaxoral® (OM-85) on frequency of upper respiratory tract infections and size of adenoid tissue in preschool children with adenoid hypertrophy”** conducted by Department of Pediatric Allergy and Immunology and Ear-Nose-Throat of Dr. Sami Ulus Maternity and Children Training and Research Hospital. The information or data obtained from your child will be compared to the information or data obtained from the other group of study.

Adenoid pad is a soft tissue like tonsil in the back of throat. A large adenoid pad is one of the most important respiratory problem in preschool children. Upper respiratory tract infections such as common cold, sore throat, swollen adenoid with infection, ear infection (otitis media) and sinusitis are commonly seen in preschool children. However, in some children who have recurrent respiratory tract infections, adenoid pad keeps growing and this can be associated with complications. Swollen (enlarged) adenoids may cause recurrent respiratory infections and each infection contributes to enlargement of adenoid pad thus promoting a vicious cycle.

Swollen adenoids can keep a child from breathing normally through the mouth or nose. If someone stops breathing for short periods during sleep, it is called “sleep apnea”. It can be dangerous. If other treatments do not help, a child might need surgery. Finally,

children with swollen adenoid and their parents might have low quality of life. In addition, it causes a burden not only for families but also for healthcare system and society due to increased health cost.

OM-85 (VAXORAL capsule) is an oral product containing the most common respiratory microbes. It acts by stimulating the child's immune system (a system that fights against microbes and diseases). Thus, with the use of Vaxoral, potential benefits can be expected, such as less respiratory infections, less antibiotics using, and preventing further growth of the adenoid pad.

The aim of this study is to investigate the effect of Vaxoral on the frequency of respiratory tract infections and size of the adenoid in children aged 2-6 years with adenoid hypertrophy.

A total of 68 children will be randomly assigned to two groups [Vaxoral capsule and placebo (capsules that have a Vaxoral appearance but no product)]. You and your doctor will not know which of your child has taken it. Three consecutive months, the first 10 days of each month, will be swallowed in the morning. After 6 months, the same treatment will be repeated for 3 months.

Whenever your child becomes sick (cold, flu, fever, sore throat) during this one year period, bring him/her to the Pediatric Allergy-Immunology Outpatient Clinic.

Muayene sonrası sizlerden (anne veya baba veya çocuğun yasal bakıcısı) hastalık belirtileri (burun akıntısı, tıkanıklık gibi), antibiyotik adı ve süresi, kreşe/ana okuluna gidememeyi size verilen kağıda (Form 1) yazmanız istenecektir.

You will be asked to write on the paper (Form 1) that is given to you (parents or the legal guardian of the child) after the examination for the disease complaints (such as nasal discharge, obstruction), antibiotic name and duration, nursery/school absenteeism.

Her 3 ayda bir sizler tarafından geniz eti ile ilgili bir anket (Form 2) doldurulacaktır. Her 3 ayda bir Çocuk Alerji-İmmunoloji Polikliniğine başvurmanız ve evde kaydettiğiniz formları getirmeniz gerekir.

Every 3 months you will be asked to fill in a questionnaire about adenoids (Form 2) and applied our Pediatric Allergy Outpatient Clinic for control.

At 6th, 9th and 12th months of the study, the size of adenoid will be assessed by the ear-nose-throat specialist using "fiberoptic flexible nasopharyngoscopy" (nose examination with a light thin tube). Depending on your child's complaints, additional "fiberoptic flexible nasopharyngoscopy" may be performed if deemed necessary.

At the end of the 12th month, a x-ray (lateral nasopharyngeal graphy) will be taken for the size of the adenoid. During x-ray exposure, it will be exposed to negligible dose of radiation.

You and your child have no responsibility for this research.

This research has no possible risks. Throughout the study period your child will be able to use nasal corticosteroids (nasal spray containing nasal cortisone), antibiotics or antihistamines as needed for swollen adenoid and infections. Vaxoral, which will be given in this study, has been used safely for children older than 6 months for many years.

Side effects with Vaxoral are fairly low. It can be seen nausea, abdominal pain, vomiting, rash, allergic reactions, cough, fever or weakness. Do not use Vaxoral when you have any of these, but you call us (doctors).

If there are any developments that may be of interest to your child during the investigation, this will be notified to you immediately. To get additional information about the study or any problem related to the study, call

No payment will be made to you because of your participation in this study; And you will not be charged for any examinations, laboratory tests and medical care services covered by this research from your social security provider.

Taking part in this study is entirely up to you. You can refuse to participate in the study or leave at any stage of the study; This will not lead to any punishment or any situation that hinders your benefits. If you fail to comply with the applicable requirements or disrupt the work schedule the investigator may remove you from the study by giving you information. The results of the research will be used for scientific purposes; If you withdraw from the study or are removed by the investigator, the medical data about you may also be used for scientific purposes if necessary.

All your medical and identification information belonging to you will be kept confidential and will not be shared with others even in the case of research publication. But

the investigator's observers, auditors, ethics committees' and governments' authorities can access your medical information as needed.

Confirmation of Participation to Work:

I have read and verbally listened to the above information which should be given to the volunteer before the investigation started. I ask all the questions that come to mind from the researcher. I have full understanding of all the explanations made to me in writing and verbally. I have been given enough time to decide if I want to participate in the study. My child was also informed verbally and in detail about the procedures and treatment to be done. Under these circumstances, I authorize the investigator to monitor, transfer and process medical information belonging to my child, and I voluntarily accept the invitation to participate in this research without any compulsion or pressure.

A signed copy of this form will be given to me.

Volunteers'

Name-surname:

Address:

Tel-Fax:

Date and signature:

For those under custody or guardianship, the parent or guardian,

Name-surname:

Address:

Phone-Fax:

Date and signature:

The researcher, who made the explanations,

Name-surname:

Position:

Address:

Phone-Fax:

Date and signature:

Organization officer witnesses, from the beginning of the proceeding to the end of the process

Name-surname:

Position:

Address:

Phone-Fax:

Study name: "Effect of Vaxoral® (OM-85) on frequency of upper respiratory tract infections and size of adenoid tissue in preschool children with adenoid hypertrophy (swollen adenoid)"

Version number: 01

Date:

Informed consent form for children with 2- 6 years old children

You know that there's a disease in your throat right now. For this reason you snore at night, you can not breathe easily, and you often become colds, sore throat. We will treat you by giving you oral medication so you do not get sick often because of your throat/adenoid disease.

The given medication will not cause any pain and it will not hurt.

If you accept, we want to get you a study.

Why did we pick you?

Because this study is done in the same way as yours, in children with swollen adenoid and frequent sickness in the throat. It may be beneficial for you to join the study and for the other children who are sick like you.

What do you expect if you join?

If you agree to participate in the study, you will be given an oral medication for your illness. This medication will not bother you. It will not cause pain. You can swallow it with water or take it in juice for 10 days in the morning.

In addition, before treatment begins, your Ear-Nose-Throat doctor will look at your throat with a thin tube with a camera, while you may feel a slight pain discomfort. In addition, the film of the throat (x-ray) will be shot. In the meantime you will not feel any pain.

Once the blood is taken from the vein, some tests will be done. There will be a slight pain when taking blood. But the nurse who will take your blood will know this job very well and will do it with little pain.

These tests are absolutely necessary tests. If we do not do it, we can not understand if there is any other medication that we should give you, and there may be a problem in the treatment of your disease.

How long will the study last?

It takes 10 days to work. During this time the medicine given to you will be drunk by your mothers once a day You will get this medicine for 10 days within 3 months and then 10 days for 3 months. In the meantime, treatment for the adenoids will continue if necessary (such as nasal spray, nasal wash, antibiotic syrup).

Do you have to join this study?

Participation in this work is entirely up to you. You can refuse to join the study at this time, or you can leave without working at any time after joining. In this regard, you should talk with your parents and decide together whether or not to participate.

If there is anything I want to ask, who can I ask?

Sormak istediğim bir şey olursa kime sorabilirim?

Your mother and father gave the necessary information about this work. You can ask them all kinds of problems, and you can also ask the doctor who is looking at you for all kinds of problems and get information.

You can call the following number 24 hours a day for more information at any time during treatment.

Dr. Serap Ozmen

Phone: