

Brief Report**Design and Recruitment for the GAP Trial, Investigating the Preventive Effect on Asthma Development of an SQ-Standardized Grass Allergy Immunotherapy Tablet in Children with Grass Pollen–Induced Allergic Rhinoconjunctivitis**

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ABSTRACT

Background: Allergic rhinoconjunctivitis is a risk factor for asthma development. Treating the underlying allergy may represent an attractive method of asthma prevention. No regulatory guidance exists in this area, and, to our knowledge, no clinical investigations meeting modern regulatory standards have been published.

Objective: The objective of this publication is to describe the rationale behind the design of and report on the recruitment for the ongoing pediatric Grazax Asthma Prevention (GAP) trial.

Methods: The trial was designed for assessment of the preventive effect of an SQ-standardized grass allergy immunotherapy tablet (AIT) on asthma development, both during treatment and after the end of treatment. (The standardized quality [SQ] procedure is a standardization procedure comprising 3 components: total potency, major allergen content, and assessment of extract complexity.) The trial design was discussed with several European Competent Authorities.

Results: The GAP trial is a multinational, parallel-group, double-blind, placebo-controlled randomized

trial. Main eligibility criteria were age of 5 to 12 years, grass pollen–induced allergic rhinoconjunctivitis, no asthma, and no overlapping symptomatic allergies. The children have been randomized 1:1 to receive the grass AIT or placebo once daily for 3 years, followed by a blinded observational period of 2 years. Asthma is assessed by the investigators according to specific diagnostic criteria, used at screening visits before randomization to exclude children with existing asthma, and evaluated at least half-yearly during the trial. Seven months of screening resulted in 812 randomized children at 101 centers in 11 countries.

Conclusions: To our knowledge, the GAP trial represents the first double-blind, placebo-controlled randomized trial to assess the preventive effect of allergen-

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specific immunotherapy on asthma development. A total of 812 children were successfully recruited into the trial. EudraCT number: 2009-011235-12. (*Clin Ther.* 2011;xx:xxx) © 2011 Elsevier HS Journals, Inc. All rights reserved.

Key words: allergy, asthma, grass, immunotherapy, prevention, tablet.

INTRODUCTION

Asthma is a potentially life-threatening condition, with ~300 million affected individuals worldwide.^{1,2} It is among the most frequent chronic diseases in childhood.³ Asthma represents a considerable burden to patients, their families, and health care organizations. Measures to prevent the development of asthma are urgently required.¹

Asthma exacerbations may be caused by a variety of triggers including allergens. Reducing trigger exposure improves asthma control and reduces medication need.¹ Epidemiological studies consistently have shown that asthma and rhinitis often coexist in the same patient, and there is increasing evidence for treating allergic rhinitis and allergic asthma as different manifestations of the same disease, following a “united airways” approach.^{4–6} Allergic rhinitis is a recognized risk factor for asthma development,^{1,7–11} and a common perception is that of the “allergic march,” in which an atopic disposition is thought to lead to different disease manifestations at different stages of the disease. For some, this starts in early childhood with atopic dermatitis and then progresses to allergic rhinoconjunctivitis (ARC), which may then progress to comorbid allergic asthma.^{7,12}

A useful strategy would be to aim measures to prevent asthma in sensitized individuals with ARC.^{1,6,12} One option could be allergen-specific immunotherapy (SIT), with children selected as the target population due to the limited amount of time that has been available for progression of their allergic disease. Results from earlier trials suggest that SIT is capable of reducing the risk of developing asthma in children with ARC.^{13–18} However, these earlier trials were all open trials, with the control group receiving symptomatic medication only. Only one of the trials, the Preventive Allergy Treatment (PAT) trial, included a post-treatment follow-up period to assess any long-term effects.^{14,15} No other trials investigating the prevention of the development of asthma are mentioned in the Allergic Rhinitis and its Impact on Asthma (ARIA)

guideline,⁷ which is the international treatment guideline within the area of SIT. The most recent reviews in this therapeutic area reveal no studies on the preventive effect of SIT on the development of asthma that are newer than the described trials.^{19,20} Hence, there is a need for double-blind, placebo-controlled randomized trials in this area, and this has been called for by both the World Allergy Organization (WAO)²¹ and the pediatric committee (PDCO) of the European Medicines Agency (EMA).²² Such a trial should include both treatment and follow-up.²² The allergy immunotherapy tablet (AIT) administration form of SIT has been demonstrated to be an effective treatment for grass pollen allergy in both adults and children,^{23–28} and disease-modifying, long-term effects on grass pollen-induced ARC have been documented for the SQ-standardized grass AIT.^{29,30} Thus, the SQ-standardized grass AIT is a candidate for preventing progression of grass pollen-induced ARC into asthma. The SQ-standardized grass AIT is currently authorized in the entire EMA region as disease-modifying treatment of grass pollen-induced rhinoconjunctivitis in adults and children aged ≥ 5 years. To obtain an additional indication of asthma prevention, it is necessary to produce clinical data meeting regulatory requirements.

An EMA regulatory guideline for the clinical development of SIT products exists³¹ but has no counterpart in other parts of the world. The EMA guideline addresses only the treatment of rhinoconjunctivitis and does not cover asthma or prevention. EMA guidance for the clinical development of asthma therapy covers treatment of asthma but does not address SIT. Prevention of asthma development is not mentioned.³² For these reasons, design of a trial to assess the preventive effect of SIT and meeting modern regulatory requirements for authorization is not trivial. The objective of the present publication is to report the design and underlying considerations for such a trial, the Grazax Asthma Prevention (GAP) trial. As we have not been able to find evidence anywhere of a similar trial, expected recruitment rates and challenges for such a trial seem unexplored. Hence, the tools used for recruitment and the recruitment results are also reported.

*Trademark: Grazax® 75,000 SQ-T/2800 BAU (ALK, Hørsholm, Denmark).

METHODS

Literature Search

International treatment guidelines within rhinitis and asthma (ARIA,⁷ Global Initiative for Asthma [GINA],³³ Practical Allergy [PRACTALL]³) have been reviewed within the area of pediatric studies of SIT and within the area of prevention by SIT of the development of asthma. The Cochrane Database of Systematic Reviews has been searched for meta-analyses in the field of SIT,^{34–36} and relevant randomized controlled trials have been identified from these meta-analyses. In the search for comparative studies in addition to those identified by the methods mentioned above, abstracts from major allergy conferences (European Academy of Allergy and Clinical Immunology [EAACI], American Academy of Allergy, Asthma & Immunology [AAAAI], American College of Allergy, Asthma & Immunology [ACAAI], and the World Allergy Congress [WAC]) from 2009 to 2011 have been screened for any news of ongoing or recently completed pediatric trials of SIT and for trials of the preventive effect of SIT on the development of asthma. Finally, review articles in the area of SIT from 2008 and onward have been identified through PubMed, by combining the search terms *allergy* and *immunotherapy*, limiting to reviews in the last 3 years and scanning the resulting titles for relevant review articles. The identified relevant review articles were studied for information on comparative studies.

Trial Design

In the process of designing the trial, the EMA regulatory guideline on the clinical development of products for SIT was studied and followed where relevant, particularly in regard to recommendations for trials designed to demonstrate the long-term effects of SIT, but also with regard to the choice of control group and availability of rescue medication.³¹ In addition, the trial design was discussed among the authors and with several European Competent Authorities. The primary topic of these discussions was criteria for asthma diagnosis. International treatment guidelines were also consulted on aspects such as relevant age group³⁷ and regarding asthma diagnosis criteria (GINA,¹ PRACTALL,³ ARIA⁷). Power calculations and eligibility considerations were based on the PAT trial.^{13–15} The methods selected for statistical analysis were based on the intention-to-treat principle of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals

for Human Use (ICH) and on recommendations in various regulatory guidelines.^{38–40}

Recruitment

A steering committee focusing on recruitment was established, in parallel with the clinical staff handling trial conduct. The steering committee comprises investigators from different countries as well as representatives of the sponsor (ALK, Denmark). Each country had a specific recruitment target and specific recruitment plans based on local legislation and previous experience from clinical trials with children and/or SIT. The employed country-specific recruitment tools are shown in the [Table](#). The plans were adjusted regularly, based on the success of different approaches and experience gained in each country and shared in the steering committee. The screening period was extended into the grass pollen season to enable recruitment of patients presenting with symptoms of ARC.

RESULTS

Ethics

Written informed consent was obtained from all parents/legal guardians before initiation of any trial-related procedures, in accordance with the Declaration of Helsinki. Assent was obtained from the children according to national legislation. The trial protocol and all amendments were approved by the relevant ethics committees and regulatory bodies in each country. The design and conduct of the GAP trial follows the principles of ICH Good Clinical Practice.

Trial Design

Overall design

The GAP trial has been designed as a multinational parallel-group, double-blind, placebo-controlled randomized trial with 1:1 randomization to once-daily double-blind treatment with grass AIT or placebo for 3 years, followed by an observational period of 2 years, with maintained blinding. The design is illustrated in [Figure 1](#).

Screening visit 1 was to take place before grass pollen season (GPS) 2010; screening visit 2 was to take place during the GPS 2010; and the randomization visit was to take place after the GPS 2010, ~2 to 8 weeks after screening visit 2. After randomization, 2 visits per year have been scheduled at intervals of ~6 months, one during the winter and one during the GPS. In addition, there will be an end-of-treatment visit 2 to 6 weeks after the GPS 2013 as well as an end-of-trial visit 2 to 6 weeks after the GPS 2015.

Table. Country-specific recruitment tools employed in the Grazax Asthma Prevention (GAP) trial.

	AT	CH	DK	FR	DE	ES	FI	NO	PL	SE	UK
Clinic and general practitioner lists/databases	×	×	×	×	×	×			×	×	×
Including contacting potential families		×		×		×	×		×		
Community advertising	×	×	×		×		×	×		×	×
Media exposure			×		×		×			×	
Study fliers and posters		×	×		×	×	×	×		×	×
Key statements (see text)			×	×			×	×			×
Investigator-focused actions		×	×	×	×	×		×			×
Contact with referral doctors	×	×	×		×	×	×	×	×	×	×
Professional networking	×				×	×			×	×	×
Advertising and information at or through											
Symposia		×		×	×	×				×	×
Pediatrician societies				×		×	×				
Patient organizations		×	×			×	×				×
Pollen websites		×	×				×	×		×	

AT = Austria; CH = Switzerland; DE = Germany; DK = Denmark; ES = Spain; FI = Finland; FR = France; NO = Norway; PL = Poland; SE = Sweden; UK = United Kingdom.

Trial Population Selection

The main inclusion criteria in the trial were as follows: children aged 5 to 12 years; a clinically relevant

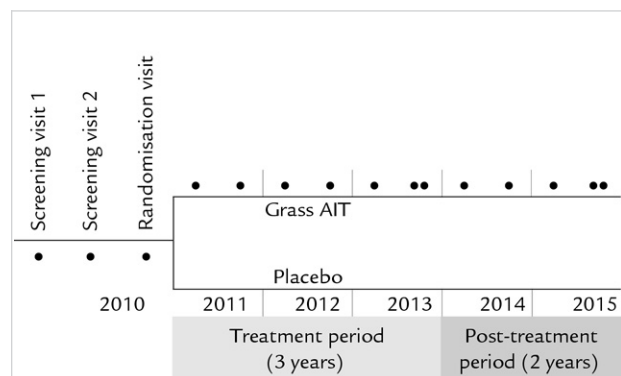


Figure 1. Grazax Asthma Prevention (GAP) trial design, 1:1 randomization. Planned visits: 3 pre-treatment visits, 1 off-season and 1 in-season visit for each treatment year and each of the 2 post-treatment years, plus 1 end-of-treatment and 1 end-of-trial visit. AIT = allergy immunotherapy tablet.

history of grass pollen-induced ARC, having received symptomatic treatment during the GPS 2009 and 2010; and positive skin prick test response (wheal diameter ≥ 3 mm) to *Phleum pratense* and positive allergen-specific immunoglobulin E (sIgE) test against *P. pratense* (IgE class 2 or higher; ≥ 0.70 kU/L).

The main exclusion criteria were a clinically relevant history of symptomatic seasonal allergic rhinitis and/or conjunctivitis caused by an allergen other than grass, overlapping the GPS; a clinically relevant history of symptomatic perennial allergic rhinitis and/or conjunctivitis caused by an allergen to which the subject is regularly exposed; inability to perform reproducible lung function tests; existing asthma or history of asthma, judged clinically by medication history and by lung function; and previous treatment by immunotherapy with grass pollen allergen or a cross-reacting allergen.

End Points

The primary end point of the GAP trial is time to onset of asthma. Secondary end points are time to onset of asthma in the GPS, asthma status (yes/no) at the

end-of-treatment and the end-of-trial visits, and average visual analogue scale (VAS) score indicating rhinoconjunctivitis symptoms.

Asthma Diagnosis

At least 1 of the following 3 minimum criteria must be met before a subject is diagnosed with asthma: (1) at least 1 episode of asthma symptoms and a documented reversibility by forced expiratory volume in the first second (FEV₁) before and after β_2 -agonist administration; (2) wheezing with or without prolonged phase of forced exhalation at physical examination and an intake of asthma medication that resulted in a clinically relevant effect; or (3) wheezing and/or prolonged phase of forced exhalation at physical examination and a documented reversibility by FEV₁ before and after β_2 -agonist administration. Furthermore, suspicion of asthma is prompted by 1 episode of wheeze and an intake of asthma medication. During screening, fulfillment of any one of the 3 criteria or suspicion of asthma led to exclusion from participation in the trial. After randomization, suspicion of asthma will have to be confirmed by 1 of the 3 minimum criteria mentioned above for the subject to be diagnosed with asthma.

In addition to the scheduled visits shown in [Figure 1](#), an unscheduled visit is to take place, in case of the child experiencing any type of asthma symptoms or taking any asthma medication. Visits outside of those pre-planned according to [Figure 1](#) may also be scheduled to confirm or disconfirm a suspicion of asthma from a previous visit. Children diagnosed with asthma will continue the half-yearly visits throughout the trial. Re-evaluation of asthma will be undertaken at all scheduled visits, to differentiate between periods with and without asthma symptoms.

Other Assessments

At screening, data on demographic characteristics, body measurements, physical examination, and medical and medication history were collected, along with data on family history of atopy and smoking. Serum levels of sIgE against *P. pratense* were assessed, and sensitizations to grass and a selection of other allergens were evaluated by skin prick test. Treatment compliance will be recorded throughout the trial, as will concomitant medication use and adverse events. For children diagnosed with asthma, the asthma control test⁴¹ will be completed at all visits following the visit at which the diagnosis is made. At all visits during the GPS, the

overall severity of the child's ARC symptoms will be assessed by the child on a VAS, and the investigator will evaluate the severity of the child's grass pollen-induced ARC according to the ARIA classification of 2008.⁷

Statistics

Power Considerations

Of 85 children in the intervention group in the PAT trial, 60 (71%) had not developed asthma after 3 years of immunotherapy. The corresponding proportion for the 78 children in the open control group was 40 children (51%).¹⁵ These proportions were used as inspiration for the GAP power calculations. The differences in design between the PAT and GAP trials were also considered: the GAP trial has a double-blind, placebo-controlled design and involves only grass pollen-allergic children, whereas the PAT trial had an open control group and involved both grass and tree pollen allergy. Taken together, these considerations led to a requirement of at least 620 randomized children in order to be able to detect a difference corresponding to a hazard ratio of ~0.5 on a 5% significance level with a power of 95%.

Statistical Testing

In the primary analysis, the treatment effect will be estimated by the hazard ratio for developing asthma. The time to onset of asthma is measured in days from randomization. For patients with no onset of asthma, the time is right-censored at the last visit before the analysis. For patients with trial discontinuation before the end-of-treatment visit, the time is right-censored at the treatment stop date. For patients with trial discontinuation after the end-of-treatment visit but before the end-of-trial visit, the time is right-censored at the date of discontinuation.

Treatment

The investigational medicinal products (IMPs) comprise active treatment or placebo. The active treatment is the SQ-standardized grass AIT, and the placebo treatment is an oral lyophilisate similar to the grass AIT in appearance, touch, smell, and taste but without grass pollen allergen. IMP treatment was to start at the randomization visit and is to continue for 3 consecutive years. The daily dose of IMP is one tablet, applied sublingually.

The children may experience ARC symptoms that require additional treatment. Furthermore, children developing asthma during the trial will be diagnosed

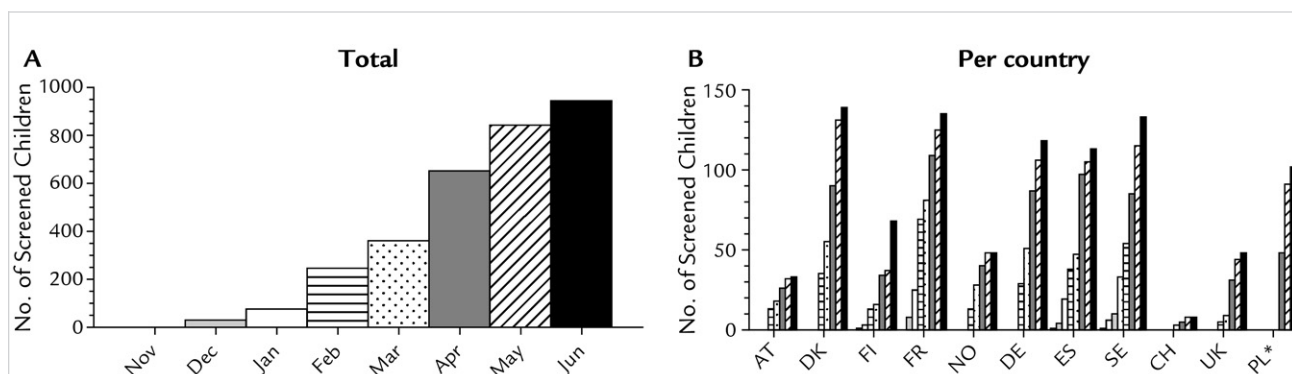


Figure 2. Total (A) and country-specific (B) Grazax Asthma Prevention (GAP) trial screening rates. Number of sites: Austria (AT), 2; Denmark (DK), 8; Finland (FI), 3; France (FR), 12; Norway (NO), 6; Germany (DE), 19; Spain (ES), 12; Sweden (SE), 8; Switzerland (CH), 3; United Kingdom (UK), 4; and Poland (PL), 12. *PL initiated as an additional country.

and treated accordingly. Rescue medication for ARC symptoms is provided at all winter visits to cover the forthcoming GPS, as a standard panel comprising loratadine tablets (10 mg) or desloratadine oral solution/syrup 0.5 mg/mL, olopatadine eye drops (1 mg/mL), and budesonide nasal spray (32/64 μ g/dose). In addition, a standard panel of asthma rescue medication will be at the investigator's disposal, comprising salbutamol for inhalation (100 μ g/dose), fluticasone for inhalation (100 μ g/dose), and prednisolone tablets (5 mg).

Recruitment

The 101 trial centers are distributed over 11 countries: Austria, Denmark, Finland, France, Germany, Norway, Poland, Spain, Sweden, Switzerland, and the United Kingdom. The first child was screened on November 24, 2009, and the screening target was met on June 21, 2010. Screening resulted in 812 randomized children. The recruitment rate varied over time and geographically, as shown in Figure 2.

DISCUSSION

In this section, the rationale behind specific choices made when designing the trial is discussed along with the main recruitment challenge and how it was addressed.

Trial Population Selection

A lower age limit of 5 years was set, as this is a standard recommended lower age limit for SIT.³⁷ The upper limit of 12 years is based on the 5-year duration of the trial, meaning that the oldest participants will be

close to adulthood at the end of the trial. Inclusion of older children would lead to logistical problems as some subjects might then have left their home during the last few years of the trial.

Because the primary end point of the trial is time to development of asthma, it is essential for the trial outcome to avoid randomizing children in whom asthma is already present. This is reflected in the exclusion criteria, with asthma assessed at 2 separate screening visits, based on experience from the PAT trial in which 20% of the children turned out to have asthma symptoms before starting their treatment.¹⁵ Also pertaining to the primary end point, children had to be able to perform reproducible lung function tests to be eligible for the trial.

Children who had received grass SIT within the past 5 years were excluded, due to the documented disease-modifying nature of such treatment. Furthermore, symptomatic perennial allergies or symptomatic seasonal allergies overlapping the GPS also led to exclusion, because allergic symptoms during the GPS would interfere with the assessment of certain end points, including rhinoconjunctivitis and asthma symptoms. Because multisensitization is common, however, it was decided to allow nonoverlapping seasonal allergies.

End Points

Although SIT is a specific treatment, the primary analysis concerns the development of asthma in general. The rigorous screening process is expected to have resulted in exclusion of all children with latent bronchial hyperreactivity. For the children randomized in

the GAP trial, the number of asthma triggers is expected to be limited. Modulating one trigger, their grass pollen allergy, is expected to lead to an overall reduction in their risk for developing asthma in general. However, to assess the specificity of the treatment in more detail, the trial also includes secondary end points to evaluate the development of asthma confined to being symptomatic during the GPS. In addition, asthma status (dormant/active) is assessed at the end of treatment and the end of the trial, to evaluate whether there is a difference between the 2 treatment groups. Finally, as a measure of long-term and sustained effect, the already documented effect of the SQ-standardized grass AIT on ARC symptoms is evaluated for trial participants as a secondary end point of average VAS scores.

Criteria for Asthma Diagnosis

The criteria for an asthma diagnosis in the GAP trial have been developed to capture the development of asthma through different indicators, since asthma is a composite disease with no single parameter being consistently observed in all cases.¹ The standardized diagnosis in the trial comprises 4 components: physical examination, medical history, medication history, and lung function tests. All 4 components are perceived as essential for the overall evaluation, and thus the asthma criteria listed in the Results section are worded as combination criteria.

The criteria aimed to address 3 purposes: prevention of randomization of children with asthma; early diagnosis of children who develop asthma during the trial (ie, determination of the time of onset); and re-evaluation of asthma during the trial (ie, asthma status).

Diagnosing asthma in children can be challenging due to different definitions of childhood asthma and a variety of existing guidelines aimed at helping to establish a correct diagnosis. In an effort to obtain uniform trial data, it was essential to set up criteria that are clinically acceptable and operational across the clinical traditions of the different countries participating in the trial. Furthermore, it was essential for the trial data to have a uniform, unequivocal definition of the exact time for onset of asthma. For this reason, the asthma diagnosis criteria were discussed extensively among the authors, with other experts, and with several European Competent Authorities. The resulting criteria represent a suggestion for a uniform, standardized method to determine the onset of pediatric asthma.

Recruitment

From what we have been able to discover by systematically surveying the literature within the therapeutic area of SIT, the GAP trial is the largest pediatric clinical trial of SIT ever conducted. In order to enroll >800 subjects, a total of 11 countries were included in the trial. The challenges and effectiveness of the various recruitment tools varied between countries. One common main challenge were parents' concerns that their children would be randomized to the placebo group of the trial for 5 years while being at risk for developing asthma, with the SQ-standardized grass AIT already being available in the European market. This challenge led to a discussion in the steering group of a set of key statements to be used by the investigators when answering the questions most frequently asked by possible participants. In these key statements, the importance of the trial was explained by the fact that there are currently no pharmacotherapy-based preventive therapies for asthma. There are indications that SIT has a preventive effect, but the data are limited. The need to use placebo was explained as being necessary to be able to distinguish the effect of the SQ-standardized grass AIT from the effect of being in the trial. The duration of 5 years was explained by the fact that the standard duration of SIT is 3 years, and in order to see long-term immunological and clinical effects, a 2-year follow-up period needed to be added. Finally, the benefit for the child being in the trial was listed as the close half-yearly follow-up by specialists in pediatric asthma and allergic disease, for a period of 5 years, as well as free symptomatic medication for ARC during the GPS and for asthma in general being provided as part of the trial regimen.

Regulatory Progress

Interestingly, the EMA PDCO has published recommendations on pediatric development for SIT since the initiation of the GAP trial. But as for the other regulatory guidance documents described earlier, these recommendations address ARC only, and prevention is not mentioned. The need for long-term studies investigating the sustained effect of immunotherapy is however a key point of the PDCO recommendations, and their proposed trial design is in accordance with the GAP trial—3 years of double-blind, placebo-controlled treatment followed by 2 years of blinded follow-up.

CONCLUSIONS

To the best of our knowledge, the Grazax Asthma Prevention (GAP) trial is the largest pediatric trial of SIT to date and represents the first double-blind, placebo-controlled randomized trial designed to conclusively test the hypothesis of a preventive effect of SIT on the development of asthma. This publication has described the trial design in detail and discussed choices made when designing the trial. Furthermore, the methods used to successfully recruit a large number of children into a 5-year placebo-controlled trial have been described.

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