PROJECT NO. 850-81
PRODUCT Pulmicort Turbuhaler®
STUDY CODE SD-004-0111
DRAFT NO. Final
DATE
(year-month-day)

Clinical Study Protocol

TITLE OF THE STUDY

START - Inhaled *S*teroid *T*reatment *A*s *R*egular *T*herapy In Early Asthma

A study of the effect of early intervention with long-term inhaled budesonide (Pulmicort Turbuhaler®) in newly diagnosed asthma.

CHAIRMAN, START STEERING COMMITTEE:

ASTRA CO-ORDINATOR:

ASTRA STATISTICIAN:

OTHER PERSONNEL	ADDRESS	RESPONSIBILITY IN THE STUDY
Clinical Research Assistant	Clinical Research & Development Medical Department I	Assistant Astra co-ordinator
Clinical Research Assistant	Clinical Research & Development Medical Department	Assistant Astra co-ordinator
CSA co-ordinator	Clinical Research & Development Clinical Safety Assessment	Responsible for the adverse event evaluation
Data co-ordinator	Clinical Research & Development Biostatistics & Data Processing	Co-ordination of Data Management

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APPENDICES

1. INTRODUCTION

Asthma is one of the most common chronic diseases world-wide and its prevalence is increasing in almost all parts of the world (1). Asthma occurs in all countries regardless of their level of development but appears to be more common in affluent than in non-affluent countries (Table 1).

Table 1

Prevalence of asthma in children

Country	Year	Age (years)	Current Asthma, (% of population)	Diagnosed Asthma (% of population)
Australia	1991	8 to 11	9,9	40,7
New Zealand	1989	12	8,1	26,6
England	1980	-	8	14,8
Germany	1990	9 to 11	4,2	7,9
Denmark	1987	7 to 16	5,3	-
Indonesia	1981	7 to 15	1,2	2,3
China	1988	11 to 17	1,2	2,4
Kenya	1991	9 to 12	3,3	11,4

It is a chronic disorder with significant impact on individuals, their families and society. Asthma can impair quality of life and be a major cause of absence from school and work. The burden of society asthma is due not only to the direct costs of the care of asthma. At least half the costs to society are indirect costs due to asthma-related morbidity, premature mortality and productivity loss (2). The intangible costs associated with the psycho-social impacts of asthma are considerable.

The increase in prevalence of asthma may be related to environmental factors. Factors considered to cause asthma are listed in Table 2.

Table 2

Causal factors

- Indoor allergens
  - Domestic mites
  - Animal allergens
  - Cockroach allergen
  - Fungi
- Outdoor allergens
  - Pollens
  - Fungi
- Occupational sensitisers

Other factors such as respiratory infections, small size at birth, diet, air pollution and passive and active tobacco smoking are considered to contribute to the development of asthma.

The pathogenesis of asthma is complex but it is now generally accepted that asthma is characterised by a chronic inflammation of the airways as the result of a sensitisation process. This chronic airway inflammation is responsible for the symptoms and physiological abnormalities of asthma (Figure 1).

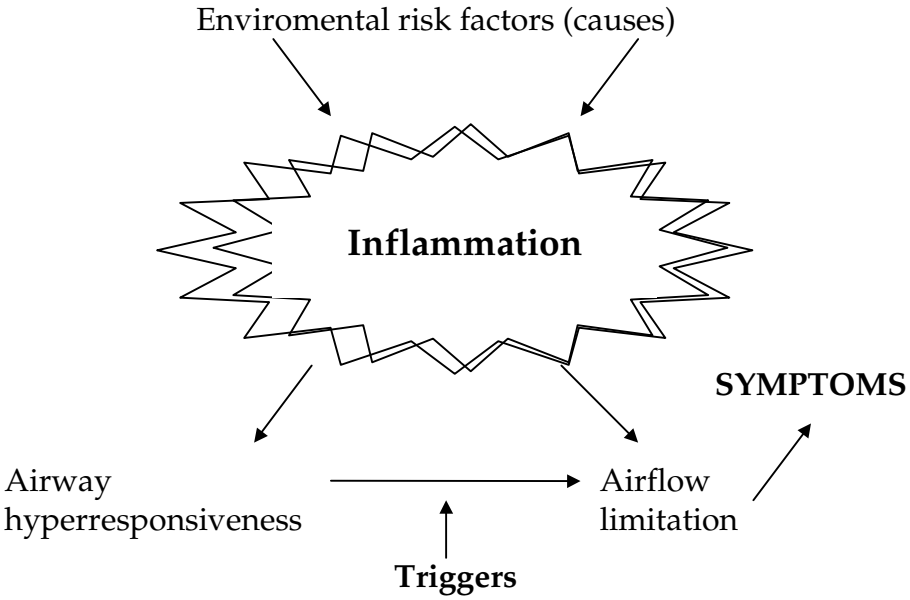


Figure 1. Mechanisms underlying asthma symptoms

The development of chronic airway hyperresponsiveness to many different triggers and airway inflammation are responsible for asthmatic symptoms and variable airflow limitation.

Long-standing asthma can lead to an irreversible disease process with persistent airway inflammation, despite complete avoidance of the causal agent. A follow-up study of occupational asthma has shown that more than half of the subjects remain symptomatic and have persistent airway hyperresponsiveness to the causal agent for at least one year after complete removal from exposure. Analysis of bronchoalveolar lavage fluid in these symptomatic subjects showed a persistent airway inflammation (3).

Asthma can also lead to irreversible airflow limitation and airway remodelling (4-6). Table 3 lists some of the features of airway remodelling observed in asthma.

Table 3

Airway remodelling in asthma
• Increase in airway smooth muscle • Vascular proliferation • Collagen deposition
• Increase in bronchial glands • Vascular congestion • Oedema formation • Cellular infiltration

Longitudinal studies have shown that only small percentages of patients with asthma become free of symptoms and have a normal airway physiology without taking chronic medication. Most patients with asthma therefore develop persistent asthma (Figure 2).

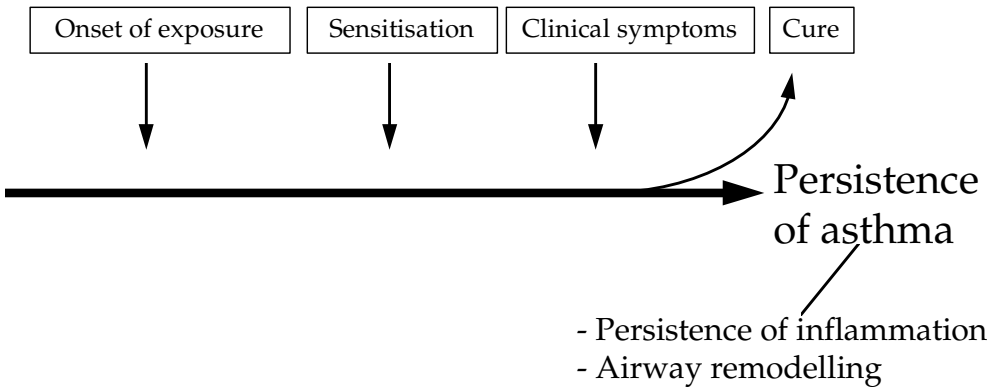


Figure 2. Natural History of Asthma

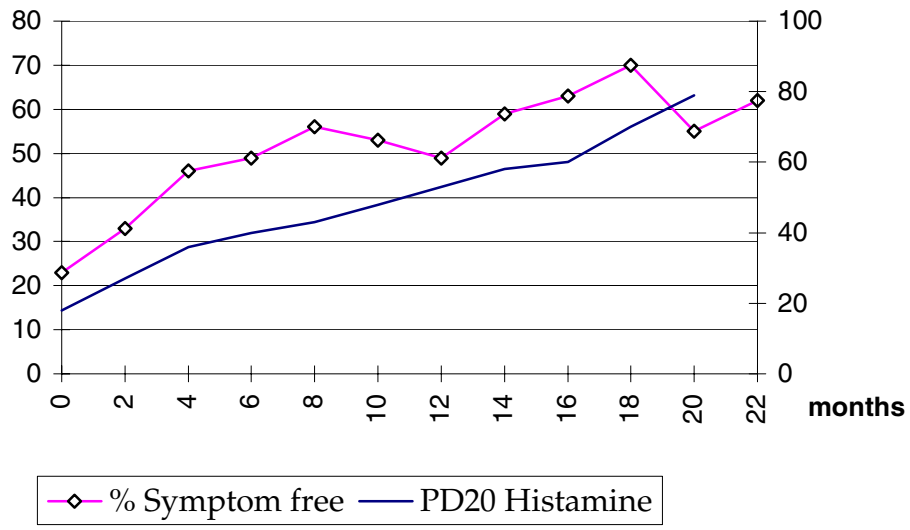
Even prolonged treatment with inhaled glucocorticosteroids does not result in a complete disappearance of symptoms and physiological abnormalities (e.g. airway hyperresponsiveness) in a substantial number of patients with asthma. This is illustrated in the 22-month study by Van Essen-Zandvliet et al. (Table 4) (7).

Table 4

Effects of 22 months' treatment with inhaled steroids on symptoms and airway responsiveness

% symptom free

Histamine/µg



The data from the van Essen-Zandvliet study suggest that irreversible or poorly reversible changes have occurred in the subjects. Similarly, stopping inhaled glucocorticosteroid treatment often results in recurrence of the disease (8, 9). This suggests that once the airway inflammation has been present for a certain time, it becomes persistent and can then only be suppressed, but not cured.

Several clinical studies have shown that inhaled glucocorticosteroids are the most effective anti-asthma treatment currently available (10, 11) and that treatment with inhaled glucocorticosteroids reduces the underlying chronic airway inflammation in asthma. However, prescription analysis shows that in almost all countries the majority of patients do not receive inhaled glucocorticosteroids as regular treatment. There may be several reasons for this, including the perceived risk of side-effects, the inconvenience of the treatment, the availability of other effective treatment, the non-availability of inhaled glucocorticosteroids, as well as the lack of convincing evidence that inhaled glucocorticosteroids are superior in the treatment of mild asthma. Indeed, therapeutic guidelines still offer a choice of therapies for mild persistent asthma (12-16).

However, delayed introduction of inhaled glucocorticosteroids in the treatment of asthma might be harmful in that this allows the disease to become persistent and remodelling of the airways to occur. Two recent studies suggest that delaying the introduction of

inhaled glucocorticosteroids in the treatment of asthma results in irreversible airflow limitation and airflow remodelling (18, 19). In a prospective study in children, Agertoft and Pedersen observed a significant relationship between the duration of asthma at the time of introduction of budesonide and the annual increase in FEV_1 during budesonide treatment (Figure 4).

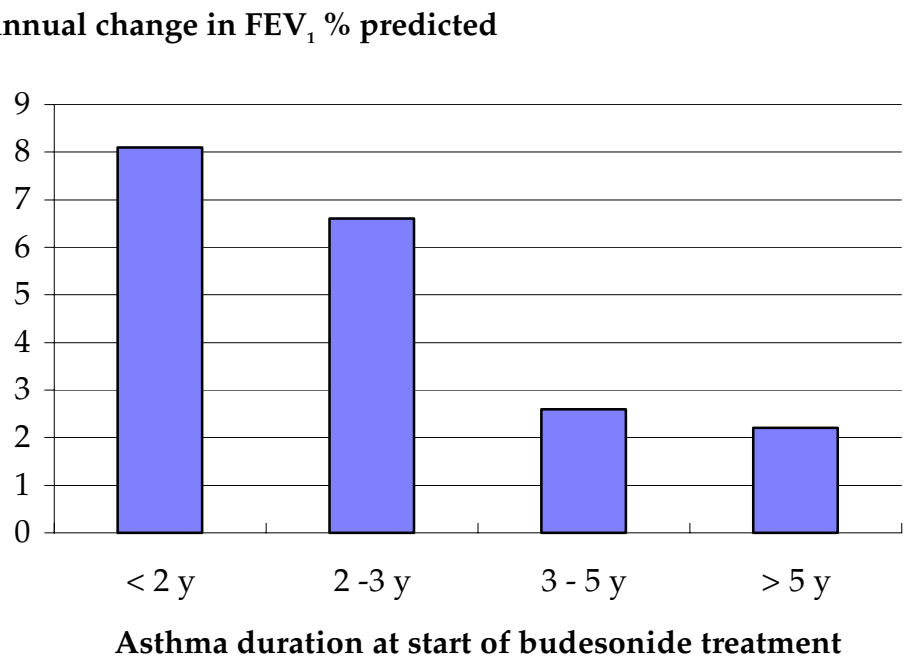


Figure 4. Effect of long-term treatment with an inhaled steroid on pulmonary function in asthmatic children.

In conclusion, our knowledge of the pathogenesis of asthma and asthmatic airway remodelling, from observations in a longitudinal study, suggests that asthma, if not treated appropriately, can be a progressive disease leading to significant irreversible airway damage. Observations on the effects of the delayed introduction of inhaled glucocorticosteroids on the underlying asthmatic airway inflammation and the lack of complete reversibility of the airway hyperresponsiveness and airflow limitation, suggest that early initiation of the treatment may influence the progression of asthma.

The START study will give the answers the following questions:

1) Does the early introduction of inhaled glucocorticosteroids, in the treatment of newly diagnosed asthma decrease the risk of severe asthma-related events?
2) Does the early introduction of inhaled glucocorticosteroids in the treatment of newly diagnosed asthma decrease the risk of the development of irreversible airflow limitation?

Additional questions that may be answered are:

1) Is an early introduction of inhaled glucocorticosteroids in the treatment of newly-diagnosed asthma a cost-effective strategy?
2) What is the evolution of newly-diagnosed asthma over time? How frequent is the evolution towards more severe asthma?
3) Is treatment with a low dose of inhaled glucocorticosteroids for several years tolerable?

2. OBJECTIVES

The primary objective of START is to evaluate if early intervention with an inhaled glucocorticosteroid (budesonide), affects the evolution of newly-diagnosed asthma.

The primary variable for the first 3 years of the study will be the time to the first severe asthma-related event. The primary efficacy variable for the whole 5 years will be the change in post-bronchodilator FEV_1 over time compared with baseline.

3. PATIENTS AND METHODS

3.1. OVERALL STUDY DESIGN

The study will be of a multi-centre, multi-national, 3-year double-blind, randomised and parallel-group design, with a 2-year, open-label follow-up. Patients will be recruited from approximately 400 centres in 30 countries world-wide.

Patients with newly-diagnosed, mild, persistent asthma will be invited to take part in this 5-year study. Patients who fulfil all of the inclusion and none of the exclusion criteria will be

randomised to receive either budesonide (Pulmicort®) or placebo via Turbuhaler® for 3-years. The study medication will be inhaled once daily, in the evening.

After 3 years of randomised treatment, all patients receive Pulmicort Turbuhaler® (budesonide) in a 2-year, open-label follow-up.

Clinic visits are planned for 6 and 12 weeks after randomisation. Thereafter the clinic visits will take place at 3-month intervals.

Interim analyses are scheduled to be performed after the last patient to be randomised has received 1 year's treatment, and then again after a further year's treatment. During these analyses a test for a statistically significant difference in severe asthma-related events between the two groups will be performed. The results from the interim analyses will be reported to the Safety Committee. Only if a highly statistically significant difference, as defined in the protocol, is found between the groups on any of these occasions, will the Safety Committee advise the Steering Committee to stop the randomised part of the study. The Steering Committee will decide on an early termination after review of the statistical and clinical significance of the findings. The Steering Committee will communicate its decision to the Safety Committee. The START Committees and their members are presented in Appendix 2.

The final analysis of data from the double-blind phase will be made when this phase has been completed. It is intended that the Case Report Forms (CRFs) and the data management system be tested before patient enrolment begins. In addition, an early check after randomisation has started will test the data management system to verify that data are flowing through the system properly.

The study outline is summarised in the figure below.

Adults: Usual therapy + budesonide 400 µg o.d. Children: Usual therapy + budesonide 200 µg o.d.	Adults: Usual therapy + budesonide 400 µg o.d. Children: Usual therapy + budesonide 200 µg o.d.

Open label design

Adults and children: Usual therapy + placebo	Adults: Usual therapy + budesonide 400 µg o.d. Children: Usual therapy + budesonide 200 µg o.d.

Years	**0**					**1**				**2**				**3**				**4**				**5**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Randomisation	x																					
History	x																					
Weight/Height	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
FEV_1/FVC	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reversibility test	x					x				x				x				x				x
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Asthma-related events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Smoking status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

3.2. PATIENTS

3.2.1. NUMBER OF PATIENTS

The intention is to randomise 6800 out-patients in order to have a sufficient number of evaluable patients. Each centre should randomise a minimum of 10 and a maximum of 50 patients. The preferable number of patients per centre is between 20 to 30. A decision to stop recruitment and randomisation will be made when the randomisation goal has been reached.

3.2.2. INCLUSION CRITERIA

1. Prior to conducting any study-related procedures, signed informed consent from patient, parent or legal guardian must be obtained. Verbal and/or signed informed consent from a child should be obtained in accordance with local guidelines (Appendix 1).

2. Out-patients of either sex, aged 6-60 years.

3. Ability to use Turbuhaler correctly as confirmed with a Turbuhaler Usage Trainer (TUT). The patient should be able to light at least two of the three indicator lamps on the TUT display (Appendix 3).

4. Asthma diagnosis made preferably within 1 year, but not more than 2 years, prior to visit 1. The diagnosis should be verified by both of the following:

4.1 ***Symptoms***; at least once a week, but not as often as every day, during the 3 months preceding visit 1, patients must have experienced one of the following:
wheeze, cough, dyspnoea, chest tightness, or night wakening due to any of these symptoms. Cough as an isolated symptom may be present every day.

4.2Reversible airway obstruction, demonstrated as historic data or assessed at visit 1 (reversibility test only), as one of the following:

A. Increase in FEV_1 of more than 12% compared with baseline, after the inhalation of a short-acting bronchodilator.

B. Exercise test: Fall in $FEV_1 \geq 15\%$ from baseline.

C. PEF variation: > 10% without bronchodilators or > 15% with bronchodilators, during 2 days within 7 consecutive days. Daily PEF variation should be calculated (per calendar day) as follows:

$$\frac{PEF\,(evening) - PEF\,(morning)}{0.5x(PEF\,(evening) + PEF\,(morning))}\,x100$$

(Bronchial hyperresponsiveness, except exercise-induced, will not be accepted as an alternative to any of the above.)

3.2.3. EXCLUSION CRITERIA

1. Symptoms compatible with the diagnosis of asthma (wheeze, cough, dyspnoea, chest tightness or night wakening) for more than 2 years prior to visit 1. (Wheezing during the first 2 years of life will not be considered a reason for exclusion).

2. Patients for whom it would be inappropriate to delay chronic treatment with glucocorticosteroids, as judged by the physician at visit 1.

3. Patients with a history of more than 30-days per year of oral or inhaled glucocorticosteroid treatment use or one depot injection per year of glucocorticosteroids irrespective of reason, within 2 years prior to study start.

4. Regular, at least once-daily, anti-asthma treatment for more than 2 years prior to visit 1.

5. Pre-bronchodilator FEV_1 <60% of predicted normal value at visit 1.

6. Post-bronchodilator FEV_1 <80% of predicted normal value at visit 1.

7. Other concomitant cardiopulmonary diseases such as:
- cystic fibrosis
- active untreated tuberculosis
- broncho-pulmonary dysplasia
- severe congenital heart disease.

8. Immunosuppressive therapy.

9. Cancer as past or present diagnosis (basal cell skin cancer is not a reason for exclusion).

10. Other concomitant diseases, including HIV/AIDS, or therapy that according to the physician could interfere with the aim of the study.

11. Hypersensitivity to budesonide or lactose intolerance.

12. Patients previously included in any other clinical study within 1 month of visit 1, or previously randomised in this study.

13. Patients with known or suspected difficulty in complying with the study protocol, due to alcohol or other drug abuse, or any other condition associated with poor compliance as judged by the investigator.

3.3. THERAPY AND DRUG HANDLING

3.3.1. STUDY THERAPY

Investigational drug:
Pulmicort Turbuhaler® 400 µg/dose, 200 doses (budesonide powder for inhalation, Astra Pharmaceutical Production,).
Pulmicort Turbuhaler® 200 µg/dose, 200 doses (budesonide powder for inhalation, Astra Pharmaceutical Production,).

Reference drug:
placebo Pulmicort Turbuhaler® 400 µg/dose, 200 doses and placebo Pulmicort Turbuhaler® 200 µg/dose, 200 doses (lactose powder for inhalation, Astra Pharmaceutical Production,).

3.3.2. TREATMENT PLAN

3.3.2.1. Dosing regimens

Treatment period (double-blind): all patients will continue with their usual anti-asthma therapy. In addition, the study medication will be inhaled once daily, in the evening.
Adults will receive 400 µg budesonide or placebo per day via Turbuhaler®.
Children (below the age of 11 years at the time of randomisation) will receive 200 µg budesonide or placebo per day via Turbuhaler®.

If a child reaches the age of 11 during the course of the study, he/she will continue on the lower dose regimen throughout both parts of the study.

Open-label period: after 3 years of randomised treatment all patients will receive budesonide via Turbuhaler®, for a 2-year period. The inhalation will be taken once daily, in the evening. Adults will receive 400 µg budesonide per day via Turbuhaler®. Children (below the age of 11 years at the time of randomisation) will receive 200 µg budesonide per day via Turbuhaler®.

3.3.2.2. Concurrent asthma therapy

At randomisation, any concurrent asthma medication, except for inhaled or systemic glucocorticosteroids, will be permitted. During the course of the study, adjustment, addition or discontinuation of concurrent medication will be accepted, if judged medically appropriate by the responsible physician. It is important that appropriate anti-asthma therapy is provided to achieve asthma control.

Every effort should be made to minimise the withdrawal of patients from the study. Changes in concurrent therapy will therefore not be a reason for withdrawal of a patient from the study.

If there is a deterioration of the asthma, as judged by the responsible physician, and the most appropriate action would be to add or increase the dose of concurrent medication, this will be permitted. This means that the use of glucocorticosteroids (inhaled

or systemic) are allowed, if the change in the patient's condition justifies this.

Therefore, during the study there will be no restrictions regarding the type or dose of concurrent anti-asthma therapy. Also, there will be no restrictions regarding the reduction, to lowest effective dose, or the withdrawal of concurrent anti-asthma therapy.

Asthma management should follow local guidelines, rules or traditions.

All concurrent anti-asthma therapy, including glucocorticosteroid therapy, must be recorded in the Case Report Form (CRF).

3.3.2.3. Duration of treatment

The study comprises a double-blind treatment period of a maximum of 3 years. Clinic visits are planned 6 and 12 weeks after randomisation. During the rest of the treatment period clinic-visits are scheduled at approximately 3-month intervals (±14 days). The visits for each patient will be scheduled to take place at about the same time of the day throughout the study.
The total duration of the study will be 5 years. Therefore, all patients who complete the study will have received budesonide for a minimum of 2 years, and half of the randomised patients will have received budesonide for a maximum of 5 years.

3.3.2.4. Continuation of treatment

After completing the study, patients will be treated according to the routines of the respective clinics. In the majority of the participating countries, Pulmicort Turbuhaler is commercially available.

3.3.3. RANDOMISATION AND STRATIFICATION PROCEDURES

Randomisation will be stratified according to age group. The two age groups are defined as: Age below 11 years, and age of 11 years or more.

Patients below 11 years of age will be allocated randomisation numbers in the range 1-9999. Patients 11 years of age or more will be allocated randomisation numbers in the range 10001-19999. Each centre will initially be allotted a whole number of tens of randomisation numbers for each age stratum. If additional randomisation numbers are needed, whole tens of randomisation numbers will then be allotted.

At the first visit the patients will be consecutively allocated enrolment codes. This will be done once the patient (for children their parent or legal guardian) has verbally agreed to participate /signed the informed consent form.

If a patient, at the first visit, fulfils all of the inclusion criteria and none of the exclusion criteria, the patient will be allocated a randomisation number from a consecutive order according to the stratification, and will be randomised into the study. The study medication corresponding to that number and treatment code will be given to the patient.

Patients can move from one centre to another and still be allowed to remain in the study if it is possible to continue the study at the new centre. If this happens during the course of the study, the patient will continue on the same randomised treatment and will have the same allocated enrolment code and randomisation number throughout the study.

3.3.4. BLINDING PROCEDURE

All study inhalers, active drug and placebo, will be of identical appearance throughout the study. The randomisation list will be known only to the person responsible for packing the medication. This person will not be involved in the study in any other way.

The first treatment pack of study medication will carry a blinded two-part, tear-off label. The detachable part of the label,

perforated for easy removal, should be detached and permanently affixed to the patient's CRF. This portion of the label will contain study code, randomisation number and visit number. The treatment information is contained in a masked panel on the label and, if it is necessary to break the blind, can be revealed by wiping the panel with an alcohol-soaked tissue.

On completion of the study, the monitor will ensure the return of the CRFs and document reasons for any code having been broken.

3.3.5. PACKAGING AND LABELLING

The packing and labelling procedure will be carried out by Clinical Pharmaceutical Supplies at Astra Draco AB. All inhalers will be labelled with "Astra Draco AB", study code, "code; 1369-1,2", randomisation number, visit number, number of doses, expiry date and name of the principal investigator. The label will also include the following information in the local language: "investigational drug", "for clinical trial", dosing instructions, "keep out of reach of children", "rinse mouth after use", "store below 30°C".

Dosing instruction on the labels:
Pulmicort Turbuhaler®/placebo Turbuhaler®: "one deep and forceful inhalation every evening", will also be translated into the local language.

Packed and labelled medication will be sent as agreed to the responsible monitor at each marketing company for transferral to the respective centres. During the study each patient will receive a maximum of 22 treatment-packs of study medication, one at each visit. Each treatment-pack will contain one Turbuhaler. Before receiving a new treatment-pack, the patient should return the previous used inhaler. All used inhalers must always be returned to the investigator.

All centres will also be supplied with a bronchodilator that should be used for all the post-bronchodilator spirometries. This will be supplied as a bronchodilator pack. The number of inhalers delivered to each centre will be dependent on the number of randomised patients at the centre.

Bronchodilator pack;
consisting of Bricanyl Turbuhaler®, 0.5 mg/dose (terbutaline sulphate, powder for inhalation, Astra Pharmaceutical Production,). In the USA, Bricanyl® pMDI, 0.25 mg/dose (terbutaline sulphate for inhalation, Ciba Geigy,) will be used.

Each bronchodilator pack will be labelled with "Astra Draco AB", centre number, study code, expiry date, "for START-related study procedures only".

Extra mouthpieces for Turbuhaler® will be supplied as well as extra adaptors for Bricanyl® pMDI.

3.3.6. DRUG ACCOUNTABILITY

All study drugs will be kept in a secure place under adequate storage conditions.

3.3.7. COMPLIANCE WITH DOSING REGIMENS

At all visits throughout the study the patients, and for children, their parent or legal guardian, will be informed that their compliance with the study dosage regimen is of great importance for the study results. At all visits inhalation technique will be checked using a Turbuhaler Usage Trainer, TUT (Appendix 3).

All centres will be supplied with extra mouthpieces for Turbuhaler®.

3.3.8. OTHER THERAPY

All prescribed medication used during this study must be recorded in the CRF.

Other medication that is considered necessary for the patient's well-being, except therapy that may interfere with the aim of the study, will be given at the discretion of the investigator.

3.3.9. PROCEDURES IN CASE OF MEDICAL EMERGENCY

The treatment code may be broken only in an emergency situation and if appropriate management of the patient necessitates knowledge of the treatment allocation.
The monitor must be notified of all situations which may require code disclosure. If the code is broken, the date, time and reason should be recorded in the patient's CRF, in the section where the tear-off-label is placed, and signed by the investigator.

Each patient will carry a Study Information Card with the name and telephone number of his/her principal investigator, treatment (budesonide/placebo), patient name and enrolment code. In the event of emergency treatment, the patient should show the Study Information Card to the treating physician. The staff involved in the present study should preferably be informed by the treating physician about the event. The patient should be asked to keep a record of the event in the Supportive Notebook (see 3.4.1).

In the event of hospitalisation due to an adverse event or severe asthma-related event, Astra personnel must be notified (Serious Adverse Event and Severe Asthma-Related Event) see 3.4.3.4 for further information.

3.4. CLINICAL ASSESSMENTS

3.4.1. CLINICAL ASSESSMENTS

Before the start of any study-related procedures, signed informed consent from patient, parent or legal guardian must be obtained. Verbal and/or signed informed consent from the child should be obtained in accordance with local guidelines (Appendix 1). The investigator will also carefully inform the patients (for children, their parent or legal guardian) about the purpose and the procedures of the study.

Clinic visits should preferably be made at the same time of the day throughout the study, with all visits falling within a time range of 5 hours. It is especially important that lung function measurements are performed at approximately the same time of the day at every visit.

At the first clinic visit, the following information will be recorded in the CRF: sex, date of birth, weight (kg),height (cm), and ethnic group. The patient will be interviewed concerning presence and duration of asthma, current anti-asthma therapy (and previous glucocorticosteroid therapy), smoking status, concomitant diseases and treatment. If a patient fulfils all of the inclusion criteria and none of the exclusion criteria, he/she will be randomised into the study at the first clinic visit.

At all scheduled visits the post-bronchodilator lung function will be assessed by spirometry, including FEV_1(*l*) and FVC (*l*). All FEV_1 and FVC measures will therefore be made after inhalation of one of the following doses of terbutaline:

- 0.5 mg terbutaline via Bricanyl Turbuhaler®
- 1 mg terbutaline via a Bricanyl pMDI.

All values should be given at B T P S.

At randomisation and thereafter yearly, a bronchial reversibility test will be performed. The patients should be instructed, if possible, to avoid short-acting inhaled bronchodilators within 6 hours and oral or long-acting inhaled bronchodilators within 24 hours before these visits. In the event that the patient does not fulfil the reversibility criterion at visit 1, historical reversibility data will be accepted.

At each visit, the patient's weight (kg) and height (cm) will be measured. Conversion tables will be available in the CRF. The patient will be asked about concurrent anti-asthma therapy (including glucocorticosteroid therapy), non-scheduled medical visits and the reasons for these, and concomitant disease and therapy. The patients will be asked to estimate the mean daily number of inhalations of short-acting bronchodilators used during the week preceding the visit. Smoking habits will be recorded.

The occurrence of asthma-related events will be monitored throughout the study. These will be evaluated and graded by the investigator and recorded in the CRFs. All patients will be offered a Supportive Notebook. The patients should be encouraged to use this Supportive Notebook to make notes on asthma-related events and asthma control between scheduled visits. Days out of work and school, use of concurrent medication and un-scheduled

medical visits, reasons for unscheduled medical visits, name and telephone number of treating physician and type of therapy that was prescribed should preferably be noted in the Notebook to refer to at clinic visits. Information noted in the Supportive Notebook will not be regarded as source data. The Notebook will not be retrieved by the investigator.

The investigator should define and grade the asthma-related events as:

Mild / Moderate:
Health care and/or pharmacy contact, since previous visit, due to asthma deterioration which does not fulfill the criteria for severe asthma.

Severe:
Hospitalisation or *emergency treatment*, since previous visit, due to worsening of asthma. Death due to asthma.

Emergency treatment is defined as:
The treatment must be given at a health care institution and the reason must be acute airway obstruction. The treatment and observation must be administered for at least 60 minutes under the supervision of a physician or a delegate. Treatment with systemic glucocorticosteroids and nebulized or parenteral bronchodilators must be given during the visit.

3.4.1.1. Health economics

Data on hospitalisation, acute therapy (including information where and how the patient was treated), drug consumption, days off work (including days off work for parents to take care of child with asthma) and school days lost will be collected from the CRF. For predictive purposes, some socio-economic questions (formal education and occupational status, and if patient is younger than 16, same questions for the child's parents) will be asked. Prices and costs will be collected from each participating country.

3.4.1.2. Other tests

Ancillary Studies
All ancillary studies must be approved by the Steering Committee. No such studies will be allowed to interfere with the main study and they should be kept to a minimum.

3.4.2. ADVERSE EVENTS (AEs)

Drug safety will be monitored by the Safety Committee chaired by , with members , , and . The committee will monitor the frequency of severe asthma-related events, the frequency of discontinuations caused by asthma and due to AEs, and the frequency of serious adverse events.

The Safety Committee will continuously be informed about the frequency of such events by Astra Draco. The Committee will receive this information divided into two treatments groups A and B, not knowing which treatment A or B represents, i.e. the real treatment codes will still be blind for the Committee.

3.4.2.1. Adverse event definition

An adverse event is:
- any unintended, unfavourable clinical sign or symptom
- any new illness or disease or deterioration of existing illness or disease
- any clinically relevant deterioration in laboratory assessments (e.g. haematological, biochemical, hormonal) or other clinical test (e.g. ECG, X-ray)

whether or not considered treatment related.

Note that the definition includes accidents and reasons for:
- changes in medication (drug and/or dose)
- medical/nursing/pharmacy consultation
- admission to hospital
- surgical operations

3.4.2.2. Serious Adverse Event definition

A serious adverse event is an adverse event which results in:

- Death
- Permanent or significant disability/incapacity
- In-patient hospitalisation or prolongation of existing in-patient hospitalisation
  (Out-patient treatment in an emergency room is not in itself a serious adverse event, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Planned hospital admissions and surgical operations for an illness or disease which existed before the drug was given or the patient was enrolled in a clinical trial are not to be considered to indicate adverse events.)

or is

- Life threatening
  ("Life threatening" means that the patient was at immediate risk of death from the adverse event as it occurred. "Life threatening" does not mean that had an adverse event occurred in a more severe form it might have caused death.)
- A congenital anomaly/birth defect

or requires

- Medical or surgical intervention to prevent permanent impairment of function or permanent damage to a body structure
  (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; other important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Medical and scientific judgement may be required.)

An adverse event fulfilling any one or more of these criteria must be reported as a Serious Adverse Event, irrespective of the dose given, and even if it is the result of an interaction or drug abuse.

Cancer will always be reported as a Serious Adverse Event as well as any experience associated with an overdose.

A distinction should be drawn between serious and severe adverse events. A severe adverse event is a major event of its type. A severe adverse event does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea but not a serious adverse event. On the other hand, a stroke which results in only a limited degree of disability may be considered a mild stroke but would be a serious adverse event.

3.4.3. PROCEDURES FOR REPORTING ADVERSE EVENTS AND ASTHMA-RELATED EVENTS

The patients will be provided with a Supportive Notebook in which they can note when asthma deterioration or changes in therapy occur. The investigator will ask the patient to review the notebook at each clinic visit with regard to any notes on adverse events and asthma-related events. The events will then be recorded on the appropriate form in the CRF by the investigator.

3.4.3.1. Adverse Event Reporting

Adverse events will be collected by means of a standard question: "Have you had any health problems or symptoms not usually associated with your asthma since your last visit?" The question will be put to each patient at visits 2-22. Spontaneously reported and/or observed AEs and the patient's response to this question will be recorded on the Adverse Event Form.

The patients will be asked to assess the intensity of the reported adverse events according to the following scale:

1= Mild; Awareness of sign or symptom, but easily tolerated.
2= Moderate; Discomfort sufficient to cause interference with normal activities.
3= Severe; Incapacitating, with inability to perform normal activities.

3.4.3.2. Reporting of Asthma-Related Events

Asthma-related events will be collected by means of the question: "Have you had any health care and/or pharmacy contact due to asthma worsening since the previous visit?" This question will be

put to all patients at each visit throughout the study (visits 2-22) The information given will be graded by the investigator according to the following:
Mild / Moderate:
health care and/or pharmacy contact, since previous visit, due to asthma deterioration which does not fulfil the citeria for severe asthma.
Severe:
Hospitalisation or *emergency treatment*, since previous visit, due to worsening of asthma. Death due to asthma.

Emergency treatment is defined as:
The treatment must be given at a health care institution and the reason must be acute airway obstruction. The treatment and observation must be administered for at least 60 minutes under the supervision of a physician or a delegate. Treatment with systemic glucocorticosteroids and nebulised or parenteral bronchodilators must be given during the visit.

Note that symptoms associated with the patient's asthma which do not require health care and/or pharmacy contact, are not to be reported in the CRF.

3.4.3.3. Discontinuations due to Adverse Events or Asthma-Related Events

Discontinuations due to adverse events and asthma-related events will be separated into two categories on the Study Termination Form.

If a patient discontinues participation in the study due to deteriorated symptoms of asthma, the reason for discontinuation should be reported as "Disease under investigation deteriorated". The event should also be reported separately on the START Safety Report.

Discontinuations due to adverse events which are not symptoms of asthma are to be reported as "Adverse Event".

3.4.3.4. Reporting of Serious Adverse Events, Severe Asthma-Related Event Reporting and discontinuation due to asthma

All serious events, all severe asthma-related events and all discontinuations due to asthma have to be reported, whether they are considered causally related to the study drug or not.

The investigator must inform the monitor or other representative **within 1 working** day of any Serious Adverse Event, Severe Asthma-related Event or discontinuation due to asthma that occurs during any part of the study (e.g. from visit 1 until the study is terminated).

In addition to the CRF, the START Safety Report must be completed and sent so that it reaches Clinical Safety Assessment at Astra Draco **within 5 calendar days**.

The investigator will be asked to assess Serious Adverse Events, Severe Asthma-related Events and discontinuation due to asthma regarding causal relationship to the study drug according to the following classifications:

1. **Probable**
   Time relationship exists. No other possible causative factor(s) exists. Improvement on dechallenge or dose reduction (if performed) has occurred. Recurrence of symptoms on rechallenge (if performed) has occurred. A specific laboratory investigation (if performed) has confirmed the relationship.

2. **Possible**
   Time relationship exists. Other possible doubtful factor(s) may exist. Improvement on dechallenge or dose reduction may or may not have been seen.

3. **Unlikely**
   Time relationship non-existent or doubtful and/or other factor(s) certain or probable to have been causative.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as unlikely.

3.4.3.5. Unresolved Adverse Events and Asthma-Related Events

If an adverse event or an asthma-related event is present when the study is terminated, its subsequent course must be followed until the event subsides or until the investigator decides that no further follow-up is necessary. However, more information about such events may be requested.

3.4.3.6. Terminology

The Astra Adverse Event Dictionary will be used for classification of the adverse drug reactions. It is based on, and follows the structure of, the WHO Adverse Reaction Terminology.

3.5. TREATMENT DISCONTINUATIONS

Patients, parent/legal guardian are free to discontinue their/their child's participation in the study at any time, and without prejudice to further treatment. Patients' participation in the study may be discontinued at any time at the discretion of the investigator.

The conditions under which a patient must be withdrawn are:

- non-cooperation, e.g. poor compliance with treatment regimen.
- withdrawal of consent by the patient or the parent or legal guardian of the child.
- erroneous inclusion.

All data obtained up to the time of withdrawal should be available for collection by the Astra monitor. When a patient, and for children, the parent or legal guardian, decides to discontinue participation in the study he/she should always be contacted in order to, if possible, obtain information about the reason(s) for discontinuation and any asthma-related events or adverse events. Whenever possible, the patient should return for a clinic visit at the time of, or soon after, discontinuation (preferably within 2 weeks) and relevant assessments should be completed (i.e. bronchial reversibility, lung function, asthma-related events and adverse events). The study drug dispensed to the patient will be collected and accounted for on the Drug Accountability Form. The investigator should inform the Astra monitor of the withdrawal as soon after discontinuation as

possible. If possible, the patient should be followed with one visit annually for the whole 5-year study period. After withdrawal from the study, i.e. after abrupt termination of study treatment, patients will be treated according to the routines of the clinic.

The reason for withdrawal must be specified on the study termination form provided. If a patient is withdrawn due to an adverse event, the Adverse Event Form must be completed and the subsequent course of the Adverse Event must be followed. If the patient is withdrawn due to worsening of asthma, the START Safety Report must be completed and its subsequent course must be followed.

3.6. EFFORTS TO CONTROL INVESTIGATIONAL PROCEDURES

3.6.1. MONITORING

The monitor will visit the clinic periodically during the study to confirm that the facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being recorded accurately in the CRFs and to provide information and support for the investigator.

An AMOS-based laptop remote data entry system will be used in the study. The Astra monitors will edit the paper CRFs and enter this edited data on-site.

The monitor will ensure that drug accountability procedures are being carried out.
Source data verification will also be performed.

A patient's medical records should indicate at least: study and patient code numbers (enrolment code and randomisation number), diagnosis(es), therapy/medications and serious adverse events. Information about visits, including non-scheduled visits, should be recorded in the hospital notes/medical records, and these should be regarded as source data.

The Astra monitor (or delegate) will be available between visits if the investigator requires information and advice.

3.6.2. TRAINING

Monitors' training meetings will be arranged by Astra Draco AB. Guidelines for monitoring of the study and editing of Case Report Forms will be established. A series of investigator meetings will be followed by training programmes for involved personnel (co-investigators, nurses, technicians) with special attention on lung function tests and handling of CRFs.

The principal investigator will ensure that appropriate training relevant to the study is given to the medical, nursing and other staff involved. Any information of relevance to the performance of this study should be forwarded to the co-investigators and other staff involved.

3.7. DATA MANAGEMENT AND EVALUATION

3.7.1. DATA MANAGEMENT

Each paper CRF will be checked and edited by the monitor on-site. In this study a remote data entry system will be used. The monitors will enter data from the CRFs into a laptop computer during clinic visits. Software dedicated to this trial and including a number of logical controls, will be used. The data files will be transferred continuously from the Astra Marketing Companies to regional centres in Australia, Singapore, Hungary, USA and Sweden. The regional centres will install and continuously maintain and support the remote data entry system. Medications, diagnosis, asthma-related events and adverse events will be coded by the regional centres before transferral to Astra Draco.

Astra Draco, as well as being a regional centre, will also control over the main AMOS database. Astra Draco will be responsible for the expertise regarding installations, general computing, data communications and PC support for the regional centres.

All data will be entered and edited in a blind mode. The treatment code will not be broken until Clean File has been declared and no editing will be allowed after this.

Prior to breaking the code, all decisions on the evaluability of all data in the statistical analysis must have been made and documented.

Data management systems and procedures will be described in a Data Management Plan.

Data validation and statistical analysis will be performed at Astra Draco AB

3.7.2. STATISTICAL CONSIDERATIONS

The primary approach to statistical analysis will be intention-to-treat analysis. Pragmatically, this means including all patients who were randomised, known to take at least one dose of study medication and on whom data are available.

Primary efficacy variables are:

- Time to the first severe asthma-related event, according to definition in 3.4.1., during the double-blind period.

- Change from baseline to the end of the open-label period in post-bronchodilator FEV_1 % predicted.

Secondary variables include:

- Number of asthma-related events during the double-blind period.

- Time to the first addition of systemic or inhaled glucocorticosteroid therapy during the double-blind period.

- Data on health care utilisation, days off work, school-days lost collected for health economic analysis.

- Change from baseline to the end of the double-blind period in post-bronchodilator FEV_1 % predicted.

- Slope of post-bronchodilator FEV_1 % predicted vs. time for the double-blind period, excluding the first 12 weeks.

Other efficacy variables to be studied include the change from baseline to each successive follow-up visit in pre- and post-bronchodilator FEV_1 % predicted.

To assess the comparability of treatment groups, baseline and demographic characteristics will be compared using descriptive statistics.

The time to the first severe asthma-related event during the double-blind period, and the time to first addition of systemic glucocorticosteroid therapy during the double-blind period, will be analysed using a log-rank test and Cox-regression analysis.

Change from baseline to the end of the open-label period, and change from baseline to the end of the double-blind period, in post-bronchodilator FEV_1 % predicted will be examined using analysis of variance and analysis of covariance. For the analysis referring to the whole study period, the intention-to-treat approach is inadequate. Instead, two alternative approaches will be taken:

1) Analysis of all patients completing at least 1 year of open-label treatment.
2) Analysis of all patients completing 2 years of open-label treatment.

Individual slopes of post-bronchodilator FEV_1 % predicted vs. time for the double-blind period, excluding the first 12 weeks, will be computed using linear regression. The individual estimates will be subjected to unweighted (each individual estimate is given the same weight) analysis of variance and analysis of covariance.

The total number and severity of asthma-related events, experienced during the double-blind period, will be analysed using chi-square methods.

Change over time in pre- and post-bronchodilator FEV_1 % predicted will be presented graphically using 95% confidence intervals.

Covariates to be considered in different analyses include country, age group (up to 11 years, 11-17 years, 18 years and above), sex, race, active smoking and pre- and post-bronchodilator FEV_1 % predicted.

For statistical analysis purposes, a common set of reference values of FEV_1 for computation of FEV_1 % predicted will be used irrespective of country and race.

Data processing will be performed at the Department of Biostatistics and Data Management, Astra Draco AB.

3.7.3. SAMPLE SIZE DETERMINATION

The risk per patient and year of a severe asthma-related event in the placebo group is assumed to be about 5% (corresponding to a median time to the first such event of about 13.5 years). We do not know of any totally relevant reference data to use, but base our assumption on an Astra study (19), where 1004 patients with mild or moderate asthma were treated during 1 year with inhaled steroids and/or inhaled beta-agonists at individual doses. In that study, 2.5% of the patients experienced an event which, although not identically defined, is comparable to a severe asthma-related event as defined in the present study. We assume that for the present study, the risk is approximately twice as high, i.e. 5%, but admit that this figure might be an overestimate.

The discontinuation rate is assumed to be at most 30% during the first year, 10% during the second year and 5% during each successive year.

According to the assumptions above 3400 patients per treatment group should be randomised in order to have 95% power to detect a 25% risk reduction in the budesonide group using a two-sided test at the 5% significance level.

If the risk in the placebo group is as low as 2.5% (median time of about 28 years), with the same number of randomised patients and using the same test, we have 95% power to detect a 35% risk reduction in the budesonide group.

With 1800 patients per treatment group after 5 years, and assuming that the standard deviation of change over time in post-bronchodilator FEV1 as % predicted is 10% units, a difference of 1.2 % units between the treatment groups in this variable can be detected at power 95% using a two-sided test at significance level 5%.

3.7.4. INTERIM ANALYSIS

An early pilot interim analysis will be conducted to validate the data management system. Results from this analysis will not be used for a decision concerning early termination of the study.

Interim analyses will be performed twice during the study, presuming that the study continues after the first interim analysis.

The first interim analysis will be made after all patients have been followed for 1 year. All data available will be used in an analysis of time to first severe asthma-related event. A significant, ($p<0.001$), difference between the groups will be a guideline for termination of the double-blind part of the study. Confidence intervals for the change in pre- and post-bronchodilator FEV_1 % predicted, visit by visit up to visit 6 (after 1 year's treatment), will also be presented.

If the study continues after the first interim analysis, a second analysis will be performed after all randomised patients have been followed for 2 years. Again, all data available will be used in an analysis of time to first severe asthma-related event. A significant, ($p<0.001$), difference will be a guideline for termination of the double-blind part of the study. Confidence intervals for the change in pre- and post-bronchodilator FEV_1 % predicted, visit by visit up to the 2 year follow-up visit, will also be presented.

The results from the interim analyses will be reported to the Safety Committee. Only if a highly statistically significant difference, as defined in the protocol, has been found between the groups on any of these occasions, will the Safety Committee advise the Steering Committee that the randomised part of the study should be stopped. The Steering Committee will decide on an early termination after review of the statistical and clinical significance of the findings. The Steering Committee will communicate its decision to the Safety Committee. The participating centres will not be notified unless a decision to terminate the study has been made.

3.7.5. HEALTH ECONOMIC ANALYSIS

The health economic analysis will be intention-to-treat analysis (including patients who are withdrawn from the blinded part of

the study). Models will be developed that will include predictions of the health economic consequences of long-term changes in lung-function. The economic models, including definition of effectiveness, how to handle drop-outs and how country specific analyses will be performed, will be defined prior to declaration of clean file for the study.

3.7.6. CRF PILOT TEST

It is intended that the CRFs and the computerised data capture system be tested in some countries prior to the main study. This is considered necessary for the development of the final data collection tools for this global trial. No study drug will be used in this test study. In addition, an early test will be made after randomisation has begun, to verify that data are flowing through the data management system properly.

3.8. ETHICAL REQUIREMENTS

3.8.1. DECLARATION OF HELSINKI AND ETHICAL REVIEW

The study will be performed in accordance with the principles stated in the Declaration of Helsinki (Appendix 5).

The study protocol, including the final version of the Patient Information and Informed Consent Form to be used, must be approved by an ethics committee before enrolment of any patients into the study. The opinion of the ethics committee should be dated and given in writing. A list of those present at the ethics committee meeting (names and positions) should be attached whenever possible. It is the responsibility of the investigator to forward to Astra before the start of the study a copy of the approval from the ethics committee clearly identifying the protocol submitted for review.

The investigator is responsible for informing the ethics committee of any serious adverse events and/or major amendments to the protocol as per local requirements. All correspondence with the committee should be filed by the investigator.

3.8.2. PATIENT INFORMATION AND CONSENT

The investigator will ensure that the patient and for the children, their parent or legal guardian is given full and adequate verbal and written information about the nature, purpose and possible risk and benefit of the study. Patients and for the children, their parents or legal guardian, must also be notified that they are free to discontinue their participation in the study at any time. The investigator is responsible for ensuring that the appropriate informed consent (Appendix 1) is obtained from all patients, and for children, from their parent or legal guardian, before conducting any study-related procedures.

The Patient Information and the Informed Consent Form are enclosed (Appendix 1). If modifications are made according to local requirements, the new version has to be approved by Astra.

A copy of the Patient Information and a copy of the Informed Consent Form should be retained by the patient, parent or legal guardian.

3.8.3. PATIENT DATA PROTECTION

Patients will only be identified by number (enrolment code and randomisation number), initials, date of birth and sex.

The principal investigator at each centre is responsible for keeping a list of all patients (who have been allocated enrolment code) including randomisation numbers, full names and last known addresses.

The patients and for children, their parent or legal guardian, should be informed in writing about the possibility of audits by regulatory authorities in which case a review of those parts of the hospital records relevant to the study may be required.

The patients and for children, their parent or legal guardian, should also be informed in writing that the results will be stored and analysed in a computer, maintaining confidentiality in accordance with local data laws.

4. FURTHER REQUIREMENTS AND GENERAL INFORMATION

4.1. INSURANCE

With respect to any liability directly or indirectly caused by the investigational drug in connection with this clinical study, Astra assumes liability in law on behalf of the investigator and his/her assistants for possible injury to the patient provided the investigator and his/her assistants have followed the instructions of Astra in accordance with this protocol and any amendments thereto, that the investigational drugs administered to the patient in this clinical study have been supplied by Astra, and that the investigator and his/her assistants have in general performed this clinical study in accordance with scientific practice and currently acceptable techniques and know-how (Appendix 6).

4.2. STUDY TIMETABLE

Patient enrolment is expected to start during the second quarter of and to be completed before the end of the second quarter . The clinical part of the study is therefore planned to be completed during mid . A draft clinical study report is planned to be available during the fourth quarter of .

4.3. CHANGES TO PROTOCOL AND RELATED PROCEDURES

No change in the study procedures shall be effected without the mutual agreement of the investigator, the Steering Committee and Astra. All changes must be documented by signed protocol amendments. If substantial changes to the design of the study are made, the regulatory authority and the ethics committee should be notified and when necessary approve the change before the inclusion of new patients.

The Astra monitor is responsible for the distribution of any amendment to the principal investigator and those concerned within the company. The principal investigator is responsible for the distribution of any amendment to all staff concerned in his/her centre and to the ethics committee.

4.4. STUDY TERMINATION

The sponsor has the right to terminate this study and remove all study material from the clinics at any time.

Reasons that may require termination of a centre include the following:

- no patients have been enrolled 6 months after study initiation
- patient enrolment is unsatisfactorily low 9 months after study initiation, i.e. less than 50% of the estimated patients have been enrolled and/or further patient enrolment cannot be ensured
- the estimated number of patients is not reached within 12 months of study initiation
- deliberate violation of the signed protocol by the clinic.

Reasons that may lead to the termination of the study include the following:

- the mean number of enrolled patients, 15 months after study initiation, is less than 75% of the estimated number
- the result of an interim analysis shows a clear difference between the two treatment groups
- the Safety Committee recommends to the Steering Committee, an early termination of the study due to safety reasons.

5. REFERENCES

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. Washington: National Institute of Health. National Heart, Lung and Blood Institute, 1995:1.

2. Davis R, Mc Tavish D. Budesonide. An appraisal of its pharmacoeconomic and quality-of-life benefits in asthma. Pharmacoeconomics 1995;7:457-70.

3. Chan-Yeung M, Leriche J, Maclean L, Lam S. Comparison of cellular and protein changes in bronchial lavage fluid of symptomatic and asymptomatic patients with red cedar asthma on follow-up examination. Clin Allergy 1988;18:359-65.

4. Kuwano K, Bosken CH, Pare PD, Bai TR, Wiggs BR, Hogg JC. Small airways dimensions in asthma and in chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;148:1220-25.

5. Seneterre E, Paganin F, Bruel JM, Michel FB, Bousquet J. Measurement of the Internal Size of Bronchi Using High Resolution Computed Tomography (HRCT). Eur Resp J 1994;7:596-600.

6. Jeffery PK, Godfrey RW, Ädelroth E, Nelson F, Rogers A, Johansson S-A. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. Am Rev Respir Dis 1992;145:890-99.

7. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 Months of Treatment with Inhaled Corticosteroids and/or Beta-2-Agonists on Lung Function, Airway Responsiveness, and Symptoms in Children with Asthma. Am Rev Respir Dis 1992;146:547-54.

8. Waalkens HJ, van Essen-Zandvliet EE, Hughes MD et al. Cessation og Long-term Treatment with Inhaled Corticosteroid (Budesonide) in Children with Asthma Results in Deteroration. Am Rev Respir Dis 1993;148:1252-57.

9. Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. N Engl J Med 1994;331:700-05.

10. Svendsen U G, Frølund L, Madsen F, Nielsen N H, Holstein-Rathlou N-H, Weeke B. A comparison of the effects of sodium cromoglycate and beclomethasone dipropionate on pulmonary function and bronchial hyperreactivity in subjects with asthma. J. Allergy Clin. Immunol. 1987;80:68-74.

11. Haahtela T, Jarvinen M, Kava T, et al. Comparison of β_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. New Engl J Med 1991;325:388-92.

12. Warner J. Asthma: a follow up statement from an international pediatric asthma consensus group. Arch Dis Child 1992;67:240-48.

13. Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. J Allergy Clin Immunol 1990;85:1098-1111.

14. British Thoracic Society, Research Unit of Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for management of asthma in adults. Chronic persistent asthma. Br Med J 1990;301:651-53.

15. Sheffer A L. National Heart, Lung and Blood Institute, National Asthma Education Programme, Expert Panel Report: guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol 1991;88:425-534.

16. Sheffer A L, Bosquet J, Busse W et al. International Consensus Report on Diagnosis and Management of Asthma. Eur Respir J 1992;5:601-41.

17. Selroos O, Pietinalho A, Löfroos A-B, Riska H. Effect of Early vs Late Intervention With Inhaled Corticosteroids in Asthma. Chest 1995;108:1228-34.

18. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373-81.

19. Clinical Report, Study No 01-7201, Turbuhaler vs. CFCs in Long-term Treatment of Asthmatics, Astra Pharma Inc. Canada.

6. SIGNED AGREEMENT OF THE PROTOCOL

6.1. SIGNATURE(S) OF INVESTIGATOR(S)

As the study protocol is finalised, we still have not knowledge of how many centres there will be in every country nor which principle investigators that will participate in the study. Therefore we will administer List of principal investigators and Signed agreement of the protocol as follows:

Every country will have an appendix for List of principal investigators and Signed agreement of the protocol, see Table of contents page 5.

List of principal investigators will be updated whenever a new centre is included in the country and a new page of Signed agreement of the protocol will then also be signed and included in the appendix. The pages in the appendix will be paginated when all the centres in the country are included. Dead-line for a centre to be included in the protocol is , centres that are included after this date will be mentioned in an amendment and these principle investigators will then also sign the protocol in this amendment.

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified in the study protocol, and according to the principles of Good Clinical (Research) Practice (GCP).

Astra study code:	SD-004-0111
Study title:	Inhaled Steroid Treatment As Regular Therapy In Early Asthma

…… ……

Date

Chairman of the Steering Committee

6.2. SPONSOR SIGNATURES

On behalf of the sponsor we agree to this protocol.

…… ……

, Astra co-ordinator Date

…… ……

, Astra Statistician Date

ASTRA
ASTRA DRACO

PROJECT NO.	850-81
PRODUCT	Pulmicort Turbuhaler®
STUDY CODE	SD-004-0111
DRAFT NO.	Final
DATE	(year-month-day)

Protocol Amendment No. 1

TITLE OF THE STUDY

START-Inhaled Steroid Treatment As Regular Therapy In Early Asthma

A study of the effect of early intervention with long-term inhaled budesonide (Pulmicort Turbuhaler®) in newly diagnosed asthma.

CHAIRMAN, START STEERING COMMITTEE

ASTRA CO-ORDINATOR: Ph. D.

ASTRA STATISTICIAN: Ph. D.

The Astra coordinator/monitor is responsible for the distribution of an amendment to the principal investigator(s) and those concerned within the company. The principal investigator is responsible for the distribution of an amendment to the Ethics Committee and all staff concerned at his/her centre. It must be clearly stated (including date of amendment) on the protocol title page that the protocol has been amended.

1. The protocol for the study is to be amended as follows:

Other personnel (page 2)

Starting February Ph. D., Clinical Research Associate and , R. N., B. Sc., Assistant Director are new members of the study team at Astra Draco. will function as assistant Astra co-ordinator and will replace being responsible Data management co-ordinator.

Countries committed in the trial (page 5)

In addition to the countries committed in the START trial as described in the clinical study protocol, starting from February Denmark is also committed in the study. Hong Kong, The Netherlands and Saudi Arabia are no longer participating in the study.

3.2.2 Inclusion criteria (page 15)

Criteria that have been changed:

4.2
C. PEF variation: > 10% without bronchodilators or >15% with bronchodilators, during 2 days within 7 consecutive days.
Daily PEF variation should be calculated (per calendar day) as follows:

$$\frac{PEF_{(evening)} - PEF_{(morning)}}{0.5x(PEF_{(evening)} + PEF_{(morning)})} x100$$

(Bronchial hyperresponsiveness, except exercise-induced, will not be accepted as an alternative to any of the above.)

New version of the criteria:

4.2
C. PEF variation: Out of a 14-day period, discard the first three days' values. Calculate PEF variability which should be > 15%.

$$PEF_{var} = \frac{(A1+A2)-(B1+B2)}{(A1+A2)} \; x100$$

A1=Highest PEF
A2=Second highest PEF

B1=Lowest PEF
B2=Second lowest PEF

(Bronchial hyperresponsiveness, except exercise-induced, will not be accepted as an alternative to any of the above.)

3.2.3 EXCLUSION CRITERIA (Clarification, page 16)

In the exclusion criteria it is stated that pre- and postbronchodilator FEV_1 at visit 1 should not be below 60% and 80% of predicted normal values, respectively.

The START Steering Committee decided on January 24 that the European Community for Coal and Steel (ECCS) reference values for percent predicted FEV_1 should be used. For adults (>18 years) this means that reference values published by Quanjer *et al*[1] will be used. For Caucasian children and adolescents (>6 years) reference values published by Quanjer *et al*[2] will be used.

Percent predicted FEV_1 for children with other ethnic origin will be adjusted according to the following correction factors:

Asian; 9 % lower
Black; 13 % lower
Others; 12 % lower

[1] Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Eur Resp J 1993;6(suppl 16):5-40.

[2] Quanjer PhH, Borsboom GJJM, Brunekreef B et al. Spirometric reference values for white European children and adolescents: Polgar revisited. Pediat Pulmonol 1995;19:135-142.

3.3.1 STUDY THERAPY (page 17)

Text that has be changed:

Reference drug:
placebo Pulmicort Turbuhaler® 400 µg/dose, 200 doses and placebo Pulmicort Turbuhaler® 200 µg/dose, 200 doses (lactose powder for inhalation, Astra Pharmaceutical Production,)

New version of the text:

Reference drug:
placebo Pulmicort Turbuhaler® **200** µg/dose, 200 doses (lactose powder for inhalation, Astra Pharmaceutical Production,)

3.3.2.3 Duration of treatment (page 19)

Text that has been changed:

The study comprises a double-blind treatment period of a maximum of three years. Clinical visits are planned 6 and 12 weeks after randomisation. During the rest of the treatment period clinic-visits are scheduled at approximately 3-month intervals (±14 days).

New version of the text:

The study comprises a double-blind treatment period of a maximum of three years. Clinical visits should be planned 6 and 12 weeks after randomisation. During the rest of the treatment period clinic-visits should be scheduled at 3-month intervals (±14 days) **according to the schedule below.**

Visit 2 (6 weeks ± 7 days after visit 1)
Visit 3 (12 weeks ± 7 days after visit 1)
Visit 4 (6 months ± 14 days after visit 1)
Visit 5 (9 months ± 14 days after visit 1)
Visit 6 (12 months ± 14 days after visit 1)
etc.

3.3.5. PACKAGING AND LABELLING (page 21)

Text that has been changed (page 22):

Bronchodilator pack;
consisting of Bricanyl Turbuhaler®, 0.5 mg/dose (terbutaline sulphate, powder for inhalation, Astra Pharmaceutical Production, In the USA, Bricanyl® pMDI, 0.25 mg/dose (terbutaline sulphate for inhalation, Ciba Geigy, will be used.

New version of the text:

Bronchodilator pack;
consisting of Bricanyl Turbuhaler®, 0.5 mg/dose (terbutaline sulphate, powder for inhalation, Astra Pharmaceutical Production, . In the USA, **Breathaire®** pMDI, 0.20 mg/dose (terbutaline sulphate for inhalation, Ciba Geneva Pharmaceuticals,) will be used.

3.4.1 CLINICAL ASSESSMENT (page 23)

The Steering Committee has decided on a meeting (May 12, 1996) that the spirometer to be used in the study will be the MicroLoop II spirometer from Micro Medical, . The software are specially designed for the study.

Criteria that have been changed:

At all scheduled visits the post-bronchodilator lung function will be assessed by spirometry, including FEV_1 (*l*) and FVC (*l*). All FEV_1 and FVC measures will therefore be made after inhalation of one of the following doses of terbutaline:

- 0.5 mg terbutaline via Bricanyl Turbuhaler®
- 1 mg terbutaline via a Bricanyl pMDI.

All values should be given at B T P S.

New version of the criteria:

At all scheduled visits the post-bronchodilator lung function will be assessed by spirometry, including FEV_1 (*l*) and FVC (*l*), **using MicroLoop II spirometer (Micro Medical, UK). The spirometer uses the Micro Medical Digital Volume Transducer which measures expired air directly at**

B T P S thus avoiding inaccuracies of temperature corrections. All FEV_1 and FVC measures will therefore be made after inhalation of one of the following doses of terbutaline:

- 0.5 mg terbutaline via Bricanyl Turbuhaler®
- 1 mg terbutaline via a **Breathaire®** pMDI.

All values should be given at B T P S.

4.1. INSURANCE (page 40/Appendix 6)

The Astra liability insurance policy, No 7192088 00, with Trygg-Hansa Industrial has changed number in the countries as described in appendix 6 (see enclosed new version of appendix 6).

Former number:
Policy No 7192088 00.

New number:
Policy No 10001

2. Reason for making the amendment:

Changes in the inclusion criteria have been made after discussions at a Workshop in London, The method for defining PEF variability in this study have been found to be less sensitive and a new definition was discussed and later also tested in both paediatric and adult populations and a better sensitivity has been found. The Steering Committee has therefore come to the conclusion that the new documentation and definition of PEF variability is to prefer.

3. Actions to be taken:

- The Case Report Form has not been revised
- Patient Information and Informed Consent Form has not been revised
- National requirement should be followed with regard to Regulatory Authorities and Ethics Committees.

4. Signed agreement to the amendment

I agree to the terms of this protocol amendment.

Study code: SD-004-0111

CHAIRMAN, START STEERING COMMITTEE DATE

On behalf of Astra, we agree to the terms of this protocol amendment.

ASTRA COORDINATOR DATE

ASTRA STATISTICIAN DATE

AstraZeneca

CLINICAL STUDY PROTOCOL AMENDMENT NO. 2

DRUG SUBSTANCE	Pulmicort Turbuhaler®
VERSION NO.	01
STUDY CODE	SD-004-0111
DATE	

FINAL

START-Inhaled Steroid Treatment As Regular Therapy In Early Asthma

CENTRES AFFECTED BY THE AMENDMENT

This amendment affects all participating centres in the study.

THE PROTOCOL FOR THE STUDY IS TO BE AMENDED AS FOLLOWS:

Other personnel (page 2 and in Amendment No. 1, page 2)

Starting from January will replace as responsible Data co-ordinator at AstraZeneca R&D . and are no longer involved. is responsible AstraZeneca R&D Lund co-ordinator and will function as Clinical Research Assistant.

3.3.8. OTHER THERAPY (page 22)

Text that has been changed:

All prescribed medication used during this study must be recorded in the CRF.

New version of the text:

All prescribed medication used during the blinded part of the study (Part A) must be recorded in the CRF. During the open-label part (Part B), only asthma medication and glucocorticosteroids (independent of reason) will be recorded.

3.4.1. CLINICAL ASSESSMENTS (page 24)

Text that has been changed:

At each visit, the patient's weight and height (cm) will be measured.

New version of the text:

At each visit during the blinded part of the study (Part A), the patient's weight and height (cm) will be measured. During the open-label part (Part B), the patient's weight and height will be measured for all patients up to 20 years of age. For patients 21 years of age and above, only the weight will be measured.

3.4.3.1. Adverse Event Reporting (page 28)

Text that has been changed:

Adverse events will be collected by means of a standard question: "Have you had any health problems or symptoms not usually associated with your asthma since your last visit?" The question will be put to each patient at visit 2-22. Spontaneously reported and/or observed AEs and the patient's response to this question will be recorded on the Adverse Event Form.

The patients will be asked to assess the intensity of the reported adverse events according to the following scale:

1=Mild; Awareness of sign or symptoms, but easily tolerated.
2=Moderate; Discomfort sufficient to cause interference with normal activities.
3=Severe; Incapacitating, with inability to perform normal activities.

New version of the text:

Adverse events will be collected by means of a standard question: "Have you had any health problems or symptoms not usually associated with your asthma since your last visit?" The question will be put to each patient at visit 2-14. Spontaneously reported and/or observed AEs and the patient's response to this question will be recorded on the Adverse Event Form.

The patients will be asked to assess the intensity of the reported adverse events according to the following scale:

1=Mild; Awareness of sign or symptoms, but easily tolerated.
2=Moderate; Discomfort sufficient to cause interference with normal activities.
3=Severe; Incapacitating, with inability to perform normal activities.

During the open label part of the study, the collection of adverse events will be restricted to serious adverse events (SAEs) and discontinuation due to adverse events (DAEs). At visit 15-22, there will be a check for the investigator to assure that SAEs and DAEs since previous visit are recorded. AEs leading to discontinuation will be recorded on the Adverse Event Form.

3.7.2. STATISTICAL CONSIDERATION (page 34)

Variable to be added:

Secondary variables include:

-Number of symptom-free days (i.e., a 24-hour period without any day- or night time asthma symptoms).

REASON FOR MAKING THE AMENDMENT:

The adverse event profile is well studied in the preceding 3-year double-blind randomised phase in comparison to placebo, and so the contribution from the open label phase of the study is judged to be of minor importance. Therefore it has been decided not to spend resources on detailed adverse event recording in the open label phase, while maintaining the Serious Adverse Events and the Discontinuation Due to Adverse Events registration.

ACTIONS TO BE TAKEN:

The Case Report Form has been revised.

Patient Information and Informed Consent Form has not been revised.

National requirements should be followed with regard to Regulatory Authorities and Ethics Committees.

SIGNED AGREEMENT TO THE AMENDMENT:

I agree to the terms of this protocol amendment.

Study code: SD-004-0111

....
DATE CHAIRMAN START STEERING COMMITTEE

On behalf of AstraZeneca R&D we agree to the terms of this protocol amendment

....
DATE COORDINATOR

....
DATE STATISTICIAN

Signed agreement to the amendment

I agree to the terms of this protocol amendment.

Study code: SD-004-0111

....
DATE ASTRAZENECA MONITOR

Signed agreement to the amendement

I agree to the terms of this protocol amendment.

Study code: SD-004-0111

Centre No.:

....
DATE PRINCIPLE INVESTIGATOR