AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort
ACTIVE INGREDIENT: Budesonide/formoterol

Study No: D5890L00018
Does Tailored Education in Asthma Care Help Improve Patient Satisfaction, Adherence, and QoL (TEACH) Trial

Developmental phase: IV
Study Completion Date: 03 January 2007
Date of Report: 05 January 2008

OBJECTIVES:

The primary objective of the study was to assess whether tailored patient education for patients on Symbicort® Turbuhaler® therapy improved patient satisfaction, adherence and Quality of Life (QoL).

The secondary objectives of this study are not summarized here but they are described in the body of the report.

METHODS:

Study design

This trial was a 6-month prospective, cluster randomized trial. The primary objective was to assess if tailored patient education for patients on Symbicort® Turbuhaler® therapy improved patient satisfaction, adherence and QoL. The trial included both a usual care group (Control) and an Educational Intervention group. Principal investigator practices located at the identical geographical location (i.e. same street address) were defined as one cluster. Prior to the initiation of the trial, all patients enrolled by principal investigator(s) randomized to the same cluster were allocated to the same study group (either Control or Educational Intervention group).

Target subject population and sample size

The target subject population was approximately 400 patients with asthma where the use of Symbicort® Turbuhaler® was appropriate and indicated. This trial was conducted as a pilot trial in principal investigator practices located in Ontario, Canada. For this pilot trial, it was decided to employ a design comprising of approximately 40 clusters, with 10 patients per cluster. The decision to have numerous clusters and relatively few patients per cluster was based on mathematical reasoning, showing that increasing the number of

clusters in a trial has greater impact on the power of the trial than increasing the cluster size.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Symbicort® Turbuhaler® (dosed according to usual clinical practice) by prescription for the duration of the trial. Refer to Symbicort® Turbuhaler® product monograph for dosing guidance. Other asthma medications could have also been prescribed as per usual practice. Batch number is not applicable (not recorded).

Duration of treatment

The duration of treatment was 6 months.

Criteria for evaluation (main measures)

Efficacy and pharmacokinetics
Primary efficacy Measures:

- Assessment of patient satisfaction after 6 months of treatment
  - Patient satisfaction with the ability to manage asthma
  - Patient satisfaction with the level of knowledge about asthma
  - Require additional tools/materials/education to better manage asthma
- Assessment of patient Quality of Life after 6 months of treatment
  - Change at 6 months in Overall Score of MiniAQLQ
  - Change at 6 months in Symptoms Score of MiniAQLQ
  - Change at 6 months in Activity Limitation Score of MiniAQLQ
  - Change at 6 months in Emotional Function Score of MiniAQLQ
  - Change at 6 months in Environmental Stimuli Score of MiniAQLQ
- Adherence to treatment during 6 months of treatment
  - End of study compliance question

Secondary and other efficacy measures are not summarized here but they are described in the body of the report.

Safety

Safety analysis included summaries of Serious Adverse Events (SAEs), Discontinuations due to Adverse Events (DAEs), Lack Of Efficacy (LOE), pregnancy and overdose.

Statistical methods

The analysis was conducted as an intent-to-treat (ITT) population defined as all randomized patients with data after randomization. All tests were performed using a two-sided alternative hypothesis. The p-values less than 5% (0.05) were considered statistically significant.

While cluster randomization trials are very useful in decreasing experimental contamination, they also present various methodological and statistical challenges.[13,14] These challenges include determining an appropriate sample size and number of clusters, using the proper unit of inference, and handling the variation both within and between clusters.[13,14]

The units of randomization (i.e. clusters) in this trial included all principal investigators practicing at a particular geographic location (i.e. same street address). The choice of this cluster definition was based on the assumption that patients belonging to these practices were likely to have similar baseline characteristics, whether the same or different principal investigators treated them.

The precision of outcome measures in a cluster randomized trial depends on two factors: the within-cluster and between-cluster variability. For a trial using cluster randomization, sample size calculations are required to take into account both factors. Moreover, while increasing the overall sample size for the trial can reduce the design effect, it is only when using expected estimates of both within-cluster and between-cluster variability that a rigorous sample size can be calculated. Since such estimates are not currently available, the sponsor decided to first conduct this pilot trial in order to collect data that will help determine an appropriate sample size and number of clusters for a much larger trial involving thousands of patients and a full statistical analysis plan.

Intra-cluster (or within-cluster) correlation is a direct consequence of the cluster randomized trial design: observations on individuals belonging to the same cluster are likely to be correlated. This translates into a reduction of the statistical efficiency relative to other trial designs (i.e. conventional RCT), which needs to be reflected in the sample size calculation, usually requiring a larger sample size.

For the pilot trial, it was decided to employ a design comprising of approximately 40 clusters, with 10 patients per cluster. The decision to have numerous clusters and relatively few patients per each cluster was based on mathematical reasoning showing that increasing the number of clusters in a trial has greater impact on the power of the trial than increasing the cluster size.[13, 15]

Generalized estimating equations (GEE) approach with appropriate link functions, and mixed effect linear regression models adjusted to account for covariates with cluster as random effect and the study group as a fixed effect, were applied to the analyses where appropriate.

Subject population

Table 1 Treatment group comparison of demographic and disease data.

		Educational Intervention N=110	Control N=50
Sex (n and % of subjects)	Female	70 (63.6)	31 (62)
	Male	40 (36.4)	19 (38)

		Educational Intervention N=110	Control N=50
Age (yrs)	Mean (SD)	49 (17.5)	46.5 (18.5)
	Range	19, 88	18, 82
Smoking status (n and % of subjects)	Non-smoker	73 (66.4)	32 (64)
	Previous or current smoker	37 (33.6)	18 (36)
# pack years	Mean (SD)	11.4 (11.5)	11.5 (15.4)
Use of current written asthma treatment plan	N (%)	27 (24.5)	3 (6)
Total no. of exacerbations in the last year	Mean (SD)	1.6 (9.6)	2.4 (2.9)
	Median	0	2
	Range	0, 100	0, 12
Total no. of night-time awakenings in the last 2 weeks	Mean (SD)	2.6 (8.5)	5.7 (11.1)
	Median	0	2
	Range	0, 84	0, 60
Average number of times per day, patients used reliever meds in the last 2 weeks	Mean (SD)	2.5 (3.7)	4.3 (8.5)
	Median	1.5	2.5
	Range	0, 28	0, 60
No. of days of absenteeism in the last year	Mean (SD)	3.1 (13.9)	1.1 (2.4)
	Median	0	0
	Range	0, 110	0, 12

Efficacy and pharmacokinetic results

The subject population precludes any strong conclusions on the results of this study. Only 160 of planned 400 subjects were recruited into the study and the treatment groups were unbalanced by a ratio of approximately 2:1 in favour of the Educational Intervention arm (110 Educational Intervention:50 Control). The discontinuation rate was approximately 50% (51% Educational Intervention arm, 44% Control arm). Therefore, no firm conclusions can be drawn from the results of this study, and the findings expressed herein should be taken to suggest trends only versus conclusive data.

There was no statistically significant difference between the Educational Intervention and Control arms with respect to subjects' satisfaction with their ability to manage their asthma at baseline or after 6 months of treatment. However, there was a trend toward greater improvement within the Educational Intervention arm relative to the Control arm with respect to the change in subjects' satisfaction with their ability to manage their asthma after 6 months of treatment when compared to baseline.

The percentage of subjects at 6 months that were satisfied or better with their current level of knowledge about their asthma condition increased in both arms. The percent

increase from baseline to 6 months was numerical greater in the Educational Intervention arm versus the Control arm, but the difference between the two arms was not statistically significant.
There was no statistically significant difference between the two arms with respect to subjects' satisfaction with their current level of knowledge about their asthma condition at baseline or after 6 months of treatment. However, there was a trend toward greater improvement within the Educational Intervention arm relative to the Control arm with respect to the change in subjects' satisfaction with their current level of knowledge about their asthma condition after 6 months of treatment when compared to baseline.
About the same proportion of subjects in the Educational Intervention arm as the Control arm felt that they required additional tools, materials, and/or education to better manage their asthma at baseline. However, after 6 months of treatment a significantly lower proportion of subjects in the Education Intervention arm versus the Control arm felt that they required additional tools, materials, and/or education to better manage their asthma.
At 6 months, about a third of Educational Intervention subjects indicated that all of the listed items (treatment plan, self education booklet, face to face education session, PIKO meter) were the most helpful to manage their asthma since enrolling in the study, and 12.3% of subjects indicated that the PIKO meter was most helpful.
There was a clinically significant improvement in subjects' health status from baseline to 6 months post enrolment in both arms. There was no statistical significant difference between the two arms for the total score or each of the domain scores of the Mini Asthma Quality of Life Questionnaire (AQLQ). There was a clinically significant change from baseline at 6 months within each group as per the primary efficacy variable as measured by the Mini AQLQ. The same trend was observed for all 4 domains of the Mini AQLQ (i.e. symptoms, activity limitations, emotional function, environmental stimuli). There was no significant difference between arms with respect to results of the Mini AQLQ at baseline or at 6 months.
Adherence to treatment by patients in the Educational Intervention group at 6 months was slightly higher than that of the Control group, but the difference was not statistically significant.
Efficacy results related to the secondary objectives of this study are not summarized here but they are described in the body of the report.

Safety results

Serious Adverse Events (SAEs), Discontinuations due to Adverse Events (DAEs), Lack of Efficacy (LOE), pregnancy and overdose were collected.

Table 2 Number (%) of subjects who had at least 1 Serious Adverse Event, Discontinuation due to Adverse Event or Lack of Efficacy in any category, and total numbers

Category of adverse event	**N (%) of subjects who experienced a Serious Adverse Event, Discontinuation due to Adverse Event or Lack Of Efficacy within each category[a]**	
	Educational Intervention (110)	**Control (50)**
Serious adverse events	2 (1.8%)	0 (0)
Serious adverse events leading to death	0 (0)	0 (0)

Category of adverse event	N (%) of subjects who experienced a Serious Adverse Event, Discontinuation due to Adverse Event or Lack Of Efficacy within each category[a]	
	Educational Intervention (110)	**Control (50)**
Serious adverse events not leading to death	2 (1.8%)	0 (0)
Discontinuations of study treatment due to adverse events	5 (4.5%)	1 (2.0%)
Lack of effect	2 (1.8%)	0 (0)
	Total number of events	
Serious Adverse events	2 (1.8%)	0 (0)
Discontinuations due to Adverse Event	5 (4.5%)	1 (2.0%)
Lack of effect	2 (1.8%)	0 (0)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.