AstraZeneca

Drug product	PULMICORT RESPULES®	**SYNOPSIS**	
Drug substance(s)	Budesonide		
Document No.			
Edition No.			
Study code	SD-004-0758		
Date	23 July 2004		

Rates of Seroconversion Following Varicella Vaccination of Asthmatic Children Between the Ages of 1 and 8 Years Treated with PULMICORT RESPULES® Versus Non-steroidal Conventional Asthma Therapy

Co-ordinating investigator

Not applicable

Study center(s)

This study was conducted at 48 centers in the USA.

Publications

None at the time of this report

Study dates		**Phase of development**
First patient enrolled	5 October 2001	IV
Last patient completed	20 October 2003	

Objectives

The primary objective was to study the effect of daily therapy with PULMICORT RESPULES® (hereafter referred to as budesonide inhalation suspension, or BIS) on the immunogenicity of a live virus (varicella) vaccine in asthmatic children between the ages of 10 months and 8 years (patients had to be 12 months of age at the time of varicella immunization).

Study design

This was an open-label, non-randomized, parallel-group, concurrent-controlled cohort study.

Target patient population and sample size

Pediatric asthma patients (n=274) between the ages of 10 months and 8 years undergoing varicella immunization who had asthma symptoms requiring the initiation or continuation of maintenance asthma therapy comprised the patient population. Patients had to be 12 months of age at the time of varicella immunization.

The percentage of patients in the study population whose Visit 2 glycoprotein enzyme-linked immunosorbent assay (gpELISA) value would be ≥5.0 was assumed to be 76% (VARIVAX® Package Insert, Merck & Co., Inc., February 2000). Therefore, it was expected that 118 patients per group were sufficient to generate a 1-sided 95% continuity-corrected confidence interval for the difference in seroconversion rates between the 2 proportions that extends 0.100 units (ie, 10%) from the observed difference in proportions. It was also expected that few of the enrolled patients would be excluded from the primary analysis. Therefore, it was planned that approximately 250 children would be enrolled (ie, approximately 125 per treatment group) to achieve the required sample size for statistical analysis.

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

Two treatments were compared with respect to their potential effects on the immunogenicity of varicella immunization: BIS and non-steroidal conventional asthma therapy (NSCAT). In this study, treatment with NSCAT was defined as the use of a leukotriene modifier, a chromone, and/or an inhaled β-agonist.

No investigational product was administered during this study. The patient's parent or guardian obtained commercially available BIS or NSCAT at the instruction of the investigator. AstraZeneca reimbursed the cost of medications.

Patients in the BIS group were required to use BIS on a daily basis, whereas patients in the NSCAT group were allowed to use these therapies on a daily basis or as needed (prn) at the discretion of the investigator. Patients in the BIS group received an approved (on-label) BIS dose (daily dose, 0.25 to 1 mg).

Duration of treatment

In both treatment arms, patients could not be immunized until they had completed 4 weeks of therapy and were at least 12 months of age. At Visit 1, patients who had completed 4 weeks of either BIS or NSCAT were enrolled in the study and received varicella immunization. Patients who had not completed 4 weeks of either BIS or NSCAT started study treatment (BIS or NSCAT) and returned for immunization at Visit 1A. Visit 1A occurred no earlier than 4 weeks after the patient started study treatment (BIS or NSCAT), and no later than 10 weeks from the day of study enrollment at Visit 1. The last study visit (Visit 2) was 6 weeks after immunization.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: the percentage of patients whose Visit 2 gpELISA value was ≥5.0 (denoting seroprotection against varicella infection) among those patients whose Visit 1 or Visit 1A gpELISA value was <5.0

- Secondary variables: comparison between treatment groups of the percentage of patients whose Visit 2 gpELISA value was ≥0.625 (corresponding to a level denoting detection of varicella antibodies) and ≥1.25 (the level below which the patient is considered seronegative).

Safety

Standard safety variables were assessed and included any adverse events (AEs), common AEs, serious AEs (SAEs), AEs causing discontinuation (DAEs), and clinically significant findings from a brief physical examination. A clinical laboratory evaluation of biological samples (hematology, clinical chemistry, or urinalysis) was not conducted. Vital signs and electrocardiograms (ECGs) were not measured. The safety population was composed of all immunized patients.

Statistical methods

The primary analysis compared treatment groups with respect to the percentage of patients whose Visit 2 gpELISA value was ≥5.0 among patients whose baseline (Visit 1 or Visit 1A) gpELISA value was <5.0. A 2-sided 90% confidence interval for this difference (ie, BIS minus NSCAT) was constructed.

The following secondary analyses were conducted for those patients whose baseline (Visit 1 or Visit 1A) gpELISA value was <5.0: (1) the percentage of patients whose Visit 2 gpELISA value was ≥0.625 was compared between treatment groups; and (2) the percentage of patients whose Visit 2 gpELISA value was ≥1.25 was compared between treatment groups. These secondary analyses were repeated in the subset of patients whose baseline gpELISA value was <0.625 and again in the subset of patients whose baseline gpELISA value was <1.25.

The gpELISA values of 0.625 and 1.25 were used for analysis since 0.625 is the lower limit of quantification of the assay used to measure varicella antibody titers, and 1.25 is the limit below which the patient is considered seronegative. Thus, the limits of 0.625 and 1.25 represent serodetection and seroconversion, respectively.

No formal hypothesis testing of safety data was planned. Safety data were summarized using descriptive statistics for each treatment group.

Patient population

The BIS and NSCAT groups were comparable for demographic characteristics and were of an age that is representative of patients likely to receive varicella immunization. The majority of

patients in either treatment group were male Caucasians. Patients in both groups were at least 12 months old at the time of immunization.

Of the 315 patients enrolled at 48 centers, 41 failed screening and were not included in the safety population. All 274 patients in the safety population were immunized and received treatment; 172 were treated with BIS and 102 with an NSCAT. In both treatment groups, most patients were immunized at Visit 1 (85% and 92% of the BIS and NSCAT groups, respectively). Patients were analyzed for seroconversion in an intention-to-treat (ITT) analysis set of 243 patients and a per-protocol analysis set of 217 patients. Patients were excluded from the ITT population because of missing gpELISA values or a baseline gpELISA value ≥5.0. Most protocol deviations resulted from the prohibited use of a study medication or the use of a prohibited concurrent medication. A total of 99% and 88% of patients in the NSCAT and BIS groups, respectively, completed the study.

The overall use of concomitant medications was higher in the BIS group compared to NSCAT group. More patients in the BIS group were treated with concomitant medications for conditions such as asthma, asthma exacerbation, reactive airway disease (RAD), wheezing, or croup.

Treatment compliance (assessed at Visit 2) in the safety population was very high in both treatment groups: 91.3% in the BIS group and 100% in the NSCAT group. The 100% compliance in the NSCAT group occurred primarily as a result of most medications in this group being taken on an as-needed (prn) basis.

The demographic characteristics of study patients and the patient populations analyzed are summarized in Table S1.

Table S1 Patient population and disposition

		BIS (n=172)	NSCAT (n=102)	Total (n=274)
Population				
N allocated to treatment (N planned)		172 (125)	102 (125)	274 (250)
Demographic characteristics (safety population)				
Sex (n and % of patients)	Male	111 (64.5)	62 (60.8)	173 (63.1)
	Female	61 (35.5)	40 (39.2)	101 (36.9)
Age at consent (years)	Mean (SD)	1.5 (1.36)	1.7 (1.78)	1.6 (1.53)
	Range	0.75 to 8.0	0.83 to 8.0	0.75 to 8.0
Age at immunization (years)	Mean (SD)	1.5 (1.38)	1.7 (1.78)	1.6 (1.54)
	Range	1.0 to 9.0	1.0 to 8.0	1.0 to 9.0

Table S1 Patient population and disposition

		BIS (n=172)		NSCAT (n=102)		Total (n=274)	
Race (n and % of patients)	Caucasian	130	(75.6)	77	(75.5)	207	(75.5)
	Black	32	(18.6)	18	(17.6)	50	(18.2)
	Asian	4	(2.3)	2	(2.0)	6	(2.2)
	Other	6	(3.5)	5	(4.9)	11	(4.0)
Disposition							
N (%) of patients who	completed	152	(88.4)	101	(99.0)	253	(92.3)
	discontinued	20	(11.6)	1	(1.0)	21	(7.7)
N analyzed for safety [a]		172		102		274	
N analyzed for seroconversion (ITT)[b]		151		92		243	
N analyzed for seroconversion (PP)[c]		132		85		217	

[a] All patients who were immunized.
[b] All patients in the safety population with a baseline (Visit 1 or Visit 1A) gpELISA value of <5.0 and for whom a Visit 2 gpELISA value was available.
[c] All patients in the ITT population who did not have a protocol deviation.
ITT, Intention-to-treat; N, Number; PP, Per-protocol.
BIS, budesonide inhalation suspension; NSCAT, non-steroidal conventional asthma therapy.

Efficacy and pharmacokinetic results

Of the 151 patients in the BIS group and 92 patients in the NSCAT group who were analyzed for seroconversion (ITT population), a seroprotective gpELISA value of ≥5.0 was achieved in 129 patients (85%) and 83 patients (90%), respectively, with a 2-sided 90% confidence interval for the BIS-NSCAT difference of -0.1173 to 0.0216.

The overall summary of the shifts in gpELISA values between baseline and Visit 2 is presented in Table S2 for the 2 treatment groups.

Table S2 Shift of gpELISA values from baseline to Visit 2 (ITT population)

Treatment	gpELISA values at Visit 1 or Visit 1A	gpELISA values at Visit 2 (n and % of patients)			
		<0.625	**≥0.625 to <1.25**	**≥1.25 to <5.0**	**≥5.0**
BIS	<0.625	1 (0.7)	1 (0.7)	19 (12.6)	114 (75.5)
(n=151)	≥0.625 to <1.25	0	1 (0.7)	0	10 (6.6)
	≥1.25 to <5.0	0	0	0	5 (3.3)
	≥5.0	0	0	0	0
NSCAT	<0.625	0	0	6 (6.5)	70 (76.1)
(n=92)	≥0.625 to <1.25	0	0	2 (2.2)	6 (6.5)
	≥1.25 to <5.0	0	0	1 (1.1)	7 (7.6)
	≥5.0	0	0	0	0

BIS, budesonide inhalation suspension; NSCAT, non-steroidal conventional asthma therapy.

Safety results

Both BIS and NSCAT were generally well tolerated for the treatment of asthma in pediatric patients undergoing varicella immunization. The reported AEs were typical for the patient population, and most were of either mild or moderate intensity. Of the AEs that were classified by the investigators as being study-related, most were attributed by the investigators to the varicella vaccine (primarily fever, agitation, and injection-site reactions). The incidence of AEs for the study period from immunization to Visit 2 was 59% in the BIS group and 52% in the NSCAT group; AE incidence for the entire study period was 66% in the BIS group and 57% in the NSCAT group. One case of varicella infection occurred in a patient from the NSCAT group. The incidence of SAEs was very low in both treatment groups. There were no deaths, other significant AEs (OAEs), or discontinuations due to AEs.

A summary of AEs in each category is presented in Table S3 for the study period between immunization and Visit 2. The most common AEs that occurred between immunization and Visit 2, as summarized by preferred term, are shown in Table S4. During this study period, the most common AEs were pyrexia, upper respiratory infections (URIs), and otitis media. For the entire study period, the most common AEs occurred in the following system organ classes: infections and infestations (primarily URIs and otitis media); and general disorders and administration-site conditions (primarily pyrexia).

No AEs related to changes in vital signs or ECGs were spontaneously reported. The percentage of patients whose results from a brief head, eyes, ears, nose, and throat (HEENT) examination and a brief lung examination shifted from normal at baseline (immunization visit) to abnormal at Visit 2 was approximately twice as high in the BIS group compared to the NSCAT group.

Table S3 Number (%) of patients who had an adverse event in any category: adverse event starting between immunization and Visit 2 (safety population)

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]		
	BIS (n=172)	NSCAT (n=102)	Total (n=274)
Any adverse events	101 (58.7)	53 (52.0)	154 (56.2)
Serious adverse events	0	1 (1.0)	1 (0.4)
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	0	1 (1.0)	1 (0.4)
Discontinuations of study treatment due to adverse events	0	0	0
Other significant adverse event	0	0	0
	Total number of adverse events[b]		
Any adverse events	209	107	316
Serious adverse events	0	1	1
Other significant adverse events	0	0	0

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

[b] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

BIS, budesonide inhalation suspension; NSCAT, non-steroidal conventional asthma therapy.

Table S4 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized in either treatment group: adverse event starting between immunization and Visit 2 (safety population)

MedDRA preferred term	BIS (n=172)		NSCAT (n=102)	
	n	(%)	n	(%)
Any event	101	(58.7)	53	(52.0)
Pyrexia	21	(12.2)	16	(15.7)
Upper respiratory tract infection, NOS	26	(15.1)	4	(3.9)
Otitis media, NOS	21	(12.2)	6	(5.9)
Vomiting	9	(5.2)	3	(2.9)
Arthropod bite	7	(4.1)	3	(2.9)

Table S4 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized in either treatment group: adverse event starting between immunization and Visit 2 (safety population)

MedDRA preferred term	BIS (n=172)		NSCAT (n=102)	
	n	(%)	n	(%)
Agitation	5	(2.9)	3	(2.9)
Diarrhea	6	(3.5)	2	(2.0)
Gastroenteritis, NOS	6	(3.5)	2	(2.0)
Viral gastroenteritis, NOS	3	(1.7)	3	(2.9)
Pharyngitis	3	(1.7)	3	(2.9)
Allergic rhinitis, NOS	3	(1.7)	3	(2.9)
Dermatitis, diaper	4	(2.3)	1	(1.0)
Sinusitis, NOS	4	(2.3)	0	

Events with a total frequency of >2% across all treatment groups are included in this table.
BIS, budesonide inhalation suspension; MedDRA, Medical Dictionary for Regulatory Activities; NSCAT, non-steroidal conventional asthma therapy; NOS, not otherwise specified.

Date of the report

23 July 2004