Synopsis – Trial SHX0712

Title of Trial

A multicentre, randomised, double-blind, placebo-controlled parallel group clinical trial to investigate the efficacy and safety of specific sublingual immunotherapy with SLITone Birch in patients with seasonal birch pollen induced rhinoconjunctivitis

Investigators

27 principal investigators participated in the trial. Prof. Dr. [redacted] ermany was appointed signatory investigator

Trial Centres

The trial was conducted at 20 centres in Germany

Publication

None

Trial Period

First subject first visit: 13 June 2005

Last subject last visit: 30 August 2006

Objectives

Primary Objective

To evaluate the efficacy of specific immunotherapy with SLITone Birch compared to placebo in subjects with birch pollen induced rhinoconjunctivitis based on the rhinoconjunctivitis symptoms score as well as the rhinoconjunctivitis medication score during the entire birch pollen season.

Secondary Objectives

To evaluate the efficacy of specific immunotherapy with SLITone Birch compared to placebo in subjects with birch pollen induced rhinoconjunctivitis based on:

- Rhinoconjunctivitis symptoms score as well as rhinoconjunctivitis medication score during the peak pollen season
- Rhinoconjunctivitis plus asthma symptom score as well as rhinoconjunctivitis plus asthma medication score during the entire as well as the peak birch pollen season
- Asthma symptom score as well as asthma medication score during the entire as well as the peak birch pollen season
- Rhinoconjunctivitis assessment by VAS in the birch pollen season and during the peak birch pollen season
- QoL in the birch pollen season and during the peak birch pollen season
- Number of well days in the birch pollen season
- Tolerability of conjunctival provocation after birch pollen season compared to baseline
- Change in immunolaboratory parameters compared to baseline
- Global assessment of rhinoconjunctivitis symptoms

To evaluate the safety and tolerability of SLITone Birch compared to placebo.

Methodology

A multi-centre, randomised, double-blind, parallel-group placebo-controlled trial. Birch pollen allergic subjects suffering from rhinoconjunctivitis with/without seasonal asthma were randomised to active SLITone Birch or placebo in single-dose containers (200 STU per dose). The subjects received treatment for approximately 9 months prior to the birch pollen season and during the birch pollen season 2006.

Number of Subjects Planned and Analysed

It was planned to enrol 220 subjects (1:1). A total of 314 subjects were screened. 88 of these were screening failures; and 226 subjects were randomised.

The disposition of subjects is tabulated below.

Treatment Group	SLITone Birch		Placebo		Overall	
	N	(%)	N	(%)	N	(%)
Screened					314	
Full Analysis Set	113	(100%)	113	(100%)	226	(100%)
Withdrawn from trial	18	(16%)	12	(11%)	30	(13%)
Reasons for withdrawal:						
Lack of efficacy			1	(<1%)	1	(<1%)
Withdrawal of consent	2	(2%)			2	(<1%)
Lost to follow-up	3	(3%)	2	(2%)	5	(2%)
Non-compliance with protocol	1	(<1%)	4	(4%)	5	(2%)
Adverse event	6	(5%)	3	(3%)	9	(4%)
Other	6	(5%)	2	(2%)	8	(4%)
Withdrawal initiated by:						
Investigator	2	(2%)	2	(2%)	4	(2%)
Subject	11	(10%)	10	(9%)	21	(9%)
Sponsor	5	(4%)			5	(2%)

N= Number of subjects
%= Percent subjects of Full Analysis Set (all randomised subjects)

Diagnosis and Main Inclusion Criteria

Male and female subjects 18-65 years of age with a clinical history of moderate to severe birch pollen induced allergic rhinoconjunctivitis of at least two seasons or more requiring symptomatic treatment during the birch pollen season; with positive skin prick test (SPT) to birch (wheal diameter ≥ 3 mm) and positive conjunctival test (CPT) response to birch (at ≤ 100,000 SQ-U/ml) and positive specific IgE against birch (≥ IgE class 2).

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number

SLITone Birch, 200 STU per single-dose container, batch no. EC-Z044.

Administered once daily preferably in the morning. The drops were to be kept under the tongue for 2-3 minutes before swallowing.

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo SLITone Birch, batch no. EC-Z040.

Administered once daily preferably in the morning. The drops were to be kept under the tongue for 2-3 minutes before swallowing.

Duration of Treatment

Approximately 9 months before the birch pollen season and during the birch pollen season 2006.

Criteria for Evaluation – Efficacy

Primary Efficacy Endpoints

- The average daily rhinoconjunctivitis symptom score as well as the average daily rhinoconjunctivitis medication score in the entire pollen season

Secondary Efficacy Endpoints

- The average rhinoconjunctivitis symptom score in the peak birch pollen season.
- The average rhinoconjunctivitis medication score in the peak birch pollen season.
- The average rhinoconjunctivitis plus asthma symptom score over the entire birch pollen season.
- The average rhinoconjunctivitis plus asthma medication score over the entire birch pollen season.
- The average rhinoconjunctivitis plus asthma symptom score in the peak birch pollen season.
- The average rhinoconjunctivitis plus asthma medication score in the peak birch pollen season.
- The average asthma symptom score over the entire birch pollen season.
- The average asthma medication score over the entire birch pollen season.
- The average asthma symptom score in the peak birch pollen season.
- The average asthma medication score in the peak birch pollen season.

Additional Efficacy Endpoints

- The average rhinoconjunctivitis VAS score over the entire birch pollen season. The scale answers the question 'How have your nasal complaints been today?' from 0 = no symptoms to 100 = severe symptoms.
- The average rhinoconjunctivitis VAS score in the peak birch pollen season.
- QoL during the entire birch pollen season according to Juniper's RQLQ, calculated for each subject as the observed total RQLQ scores each week of the entire birch pollen season.
- QoL during the peak birch pollen season according to Juniper's RQLQ, calculated for each subject as the observed total RQLQ scores each week of the peak birch pollen season.
- % of well days[1] during the entire birch pollen season.
- % of well days during the peak birch pollen season.
- Difference from baseline in the conjunctival provocation threshold dose.
- Difference from baseline in immunolaboratory parameters.
- Global assessment of rhinoconjunctivitis symptoms.
- Global improvement

In addition to the efficacy endpoints mentioned in the trial protocol a more clinically intuitive endpoint is introduced. The endpoint is binary dividing the subjects into excellent rhinoconjunctivitis control or not. "Excellent rhinoconjunctivitis control" is defined as more than 50% "well days" in the entire birch pollen season.

Criteria for Evaluation – Safety

- Adverse events
- Findings from physical examinations
- Vital signs
- FEV_1
- Global assessment of tolerability

[1] A well day is defined as a day without any intake of rescue medication as well as a rhinoconjunctivitis score of 0.

Statistical Methods

The following analysis sets were used:

- Full analysis set (FAS): All subjects randomised following the Intent To Treat (ITT) ICH principle.
- Per protocol analysis set (PP): All subjects who did not have major protocol deviations.

Suggested protocol deviations were:

- Incorrect administration of the trial medication, non-attendance at trial assessments
- Non-compliance with the diary if it significantly effects the outcome of the data

Consequently it was decided that the PP analysis set comprised subjects who:

- Did not take prohibited medication
- Had sufficient pre-seasonal treatment defined as at least 7 month treatment prior to start of the pollen season
- Had sufficient trial drug compliance defined as at least 75% of drug compliance, i.e. number of single dose containers used compared to number of treatment days
- Provided sufficient diary data defined as at least 50% of diary data in the pollen season

Primary Efficacy Analysis

The endpoints are the average rhinoconjunctivitis symptom score as well as the average rhinoconjunctivitis medication score. As there are two comparisons to be evaluated the approach to this multiple comparisons issue is a hierarchical ordering of the null hypotheses. Hence, no statistical conclusions are based on test of a null hypothesis that has a rank lower than or equal to the null hypothesis that was the first not to be rejected.

The ranking of the null hypotheses will be as follows:

- SLITone Birch versus placebo on rhinoconjunctivitis symptom score
- SLITone Birch versus placebo on rhinoconjunctivitis medication score

As the ranking of null hypotheses is pre-specified no formal adjustment of the statistical significance is necessary.

The analysis is done via an ANOVA with the average rhinoconjunctivitis symptom score or the average rhinoconjunctivitis medication score as response variable and treatment group as a fixed effect and combination of centre/site and pollen region as random effects as well as adjusting for different error variation for each treatment group. 2-sided 95%-confidence intervals and p-values are presented.

Secondary Efficacy Analysis

Without adjustment for multiplicity or ranking of test all secondary efficacy analyses, except the RQLQ analysis, the last part of Global Evaluation and the “excellent rhinoconjunctivitis control”, are carried out the same way as the primary efficacy analysis.

The weekly overall RQLQ analysis is analysed using a repeated measurement ANOVA including treatment group as a fixed effect and a combination of centre and pollen region as random effects as well as adjusting for week and subject variation.

The first part of the global evaluation (by the subject Visit 7) with the 6 rhinoconjunctivitis symptoms scored 0 to 3 is analysed in the same manner as the primary efficacy analysis only this time also including assessment of season 2005 as covariate (assessed at Screening).

The second part of the Global Evaluation (by the subject) is tabulated with all 5 categories (much better, better, the same, worse, much worse). The data are analysed as an ordered categorical variable in a proportional odds regression and furthermore prior to statistical analysis the responses will be categorised as:

Improvement = Much better or Better
No improvement or worsening = The same or Worse or Much Worse

The Global Evaluation and the “excellent rhinoconjunctivitis control” are both binary outcomes and are analysed accordingly using a generalised linear mixed model with a logit link funktion.

The Global Evaluation (by the investigator) is tabulated with all 7 categories and is analysed in the same manner as the second part of the Global Evaluation by the patient.

Demography of Trial Population

Baseline characteristics for all subjects in the FAS analysis set are shown below:

Treatment Group	SLITone Birch	Placebo	Overall
	N	N	N
Number of Subjects	113	113	226
Sex			
Men (%)	44 (38.9)	42 (37.2)	86 (38.1)
Women (%)	69 (61.1)	71 (62.8)	140 (61.9)
Age (Years)			
Mean (SD)	39.3 (10.9)	39.5 (11.5)	39.4 (11.2)
Median	39.0	39.0	39.0
Q25% - Q75%	31.0-47.0	30.0-48.0	31.0-48.0
Min-max	19.0-64.0	19.0-64.0	19.0-64.0
Ethnic Origin			
Caucasian (%)	111 (98.2)	109 (96.5)	220 (97.3)
Asian (%)	1 (0.9)	2 (1.8)	3 (1.3)
African (%)		1 (0.9)	1 (0.4)
Other (%)	1 (0.9)	1 (0.9)	2 (0.9)
Smoking			
Never smoked	73 (64.6)	64 (56.6)	137 (60.6)
Currently smoking	20 (17.7)	19 (16.8)	39 (17.3)
Stopped smoking	20 (17.7)	30 (26.5)	50 (22.1)
Severity of Birch Pollen Induced Rhinoconjunctivitis			
Mild (%)	-	1 (0.9)	1 (0.4)
Moderate (%)	59 (52.2)	58 (51.3)	117 (51.8)
Severe (%)	54 (47.8)	54 (47.8)	108 (47.8)
Birch Pollen Induced Rhinoconjunctivitis (Years)			
Mean (SD)	15.8 (9.0)	14.4 (8.8)	15.1 (8.9)
Median	15.0	12.0	14.0
Q25% - Q75%	9.0-22.0	7.0-20.0	8.0-21.0
Min-max	2.0-41.0	1.0-41.0	1.0-41.0
Severity of Birch Pollen Induced Asthma			
Mild (%)	9 (8.0)	11 (10.0)	20 (9.0)
Moderate (%)	6 (5.0)	4 (4.0)	10 (4.0)
Severe (%)	-	-	-
Birch Pollen Induced Asthma (Years)			
Mean (SD)	10.4 (8.2)	6.0 (3.7)	8.1 (6.6)
Median	7.5	6.0	6.0
Q25% - Q75%	3.0-18.0	3.0-10.0	3.0 (10.0)
Min-max	1-24	0-11	0-24

N= Number of subjects

%= Percent of subjects

Efficacy Results

Primary Efficacy Endpoints

- No statistically significant differences were found between the SLITone Birch group and the placebo group in the rhinoconjunctivitis symptoms score and in the rhinoconjunctivitis medication score.
- Post hoc analysis of the primary efficacy endpoints demonstrated advantages in favour of SLITone Birch when introducing a baseline. This was also confirmed by post hoc analyses using stratification of pollen count levels and adjustment of scores based on birch pollen counts.

Secondary Efficacy Endpoints

- The endpoint "global improvement of rhinoconjunctivitis symptoms assessed by the subjects" was statistically significant in favour of SLITone as compared to placebo ($p=0.0386$).
- In the analyses of the immunological parameters IgE and IgE-blocking antibodies, a significant immunological response in subjects treated with SLITone Birch was revealed:
    - In the SLITone Birch group there was an initial rise in specific IgE of more than 50%, which levelled out over time. For the placebo group there was, as expected, minor seasonal variations in the levels of specific IgE during the trial. The IgE values in the two treatment groups were identical at treatment initiation, whereas the SLITone Birch treated group exhibited significantly higher specific IgE values ($p<0.0001$) than the placebo group at all other time points during the trial, except at the post-seasonal visit (visit 7), where the difference was no longer significant.
    - A decrease of approximately 10% in the IgX ratio was observed in the SLITone Birch group during the trial (indicating a higher IgE-blocking capacity), whereas the levels of IgX did not change considerably in the placebo group. The IgX values in the two treatment groups were identical at treatment initiation, whereas the IgX values in the SLITone Birch group were significantly lower than in the placebo group from visit 5 (after approximately 7-8 months of treatment) and throughout the trial ($p=0.015$ for visit 5, $p=0.001$ for visit 6 and $p=0.0001$ for visit 7).
- No statistically significant differences were found between the SLITone Birch and the placebo treated subjects for other secondary endpoints.

Safety Results

- Treatment with SLITone Birch was generally well tolerated
- The most frequently reported adverse events related to treatment were mild local reactions in eye, mouth or nose – primarily oral pruritus
- None of the six serious adverse events were related to treatment
- Nine subjects withdrew due to 14 adverse events – 6 subjects in the SLITone Birch group due to 10 adverse events and 3 subjects in the placebo group due to 4 adverse events.
- The tolerability of the trial medication was for the majority of subjects judged to be very good or good
- No safety concerns were observed for vital signs or physical examination

Conclusions

- The endpoint "global improvement of rhinoconjunctivitis symptoms assessed by the subjects" was statistically significant in favour of SLITone as compared to placebo.
- A significant immunological response was demonstrated for subjects treated with SLITone Birch indicating that treatment with SLITone Birch modulates the immune system in subjects with allergy to birch pollen.
- No statistically significant differences were found between SLITone Birch and placebo regarding the primary efficacy endpoint.
    - Post hoc analysis of the primary efficacy endpoints demonstrated advantages in favour of SLITone Birch when introducing a baseline. This was also confirmed in post hoc analyses using stratification of pollen count levels and adjustment of scores based on birch pollen counts.
- The trial design was based on treatment prior to and during a single birch pollen season. Clinical improvement following treatment with immunotherapy is thought to be a consequence of different immunological mechanisms that develop over time. Thus, even though clear immunological changes were observed in this trial it appears that the treatment time was too short to reach full clinical effect.
- Treatment with SLITone Birch was generally well-tolerated. The most frequently reported adverse events related to treatment were mild local reactions in eye, mouth or nose – primarily oral pruritus. No treatment-related serious adverse events occurred during the trial.

Date of the Report

Final version, 7 January 2008

This trial was conducted in compliance with the principles of ICH Good Clinical Practice.