Integrated Clinical Trial Report

A multicentre randomised Phase II clinical pilot study to compare the pharmacodynamic efficacy and tolerability of the sublingual and the vestibular administration route for SLITone$^{PLUS®}$ Birch

Investigational Medicinal Product:	SLITone$^{PLUS®}$ Birch
Clinical Trial ID:	SP-B-02
EudraCT No.:	2009-014580-39
Development Phase:	Phase II
Indication:	Birch pollen induced allergic rhinoconjunctivitis
First subject first visit:	18 January 2010
Last subject last visit:	03 January 2011
Investigator:	Coordinating Investigator: Prof. Dr. Dr. med. [redacted]
Trial Centres:	4 centres in DE
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This trial was conducted in compliance with the principles of ICH Good Clinical Practice.

Synopsis – Trial SP-B-02

Title of Trial
A multicentre randomised Phase II clinical pilot study to compare the pharmacodynamic efficacy and tolerability of the sublingual and the vestibular administration route for SLITone$^{PLUS®}$ Birch

Coordinating Investigator
Prof. Dr. Dr. med. [redacted]

Trial Centre
1. Prof. Dr. Dr. med. [redacted]
2. Prof. Dr. med. [redacted]
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Publication
None

Trial Period
First subject first visit –18 January 2010
Last subject last visit – 03 January 2011

Objectives
To compare the vestibular administration route of SLITone^{PLUS} with the sublingual route in adult subjects suffering from birch pollen induced rhinoconjunctivitis.

Methodology
A multicentre, parallel group, 1:1 randomised Phase II non-inferiority trial with central treatment allocation to one of two administration routes and single blind determination of the primary pharmacodynamic endpoint.

Number of Subjects Planned and Analysed
64 planned
86 enrolled
71 randomised
71 treated (Sublingual: 38; Vestibular: 33)
63 completed (Sublingual: 33; Vestibular: 30)
8 withdrawn
- Adverse events : 4 (Sublingual: 1; Vestibular: 3)
- Non-compliance: 2 (Sublingual: 2)
- Other reason : 2 (Sublingual: 2)

71 analysed (Sublingual: 38; Vestibular: 33)

Main Selection Criteria
Male and female subjects 18 – 65 years who have given written informed consent, with the following main inclusion criteria:
- A clinical history of birch pollen induced allergic rhinoconjunctivitis of two years or more requiring treatment during the birch pollen season
- Lack of adequate relief with symptomatic medication during the previous pollen season
- Positive Skin Prick Test (SPT) response to *Betula verrucosa* (wheal diameter ≥ 3 mm) currently performed or not older than 60 days before screening
- Positive specific IgE against *Betula verrucosa* (IgE Class ≥ 2).

Investigational Medicinal Product, Dose and Mode of Administration, Batch Number
SLITone^{PLUS} / vestibular route of administration [Group V]
(1 MonoDose per day; oral – vestibular route of administration; batch numbers D1615, E0237)

Reference Therapy, Dose and Mode of Administration, Batch Number
SLITone^{PLUS} / sublingual route of administration [Group S]
(1 MonoDose per day; oral – sublingual route of administration; batch numbers D1615, E0237)

Duration of Treatment
36 weeks

Criteria for Evaluation – Pharmacodynamics
Primary endpoint: Immunological changes from baseline in spec. IgE-blocking factor against *Betula verrucosa* after 36, (24, 12, 8, 4) weeks of treatment with SLITone^{PLUS}.
Secondary endpoints: In analogy spec. IgE and spec. IgG_4.

Criteria for Evaluation – Safety
Secondary endpoint: Incidences of the following local reactions related to the administration route: oral pruritus, oedema mouth, oropharyngeal swelling, pharyngeal oedema, swollen tongue, glossodynia.

Adverse events (AE): All AEs; AEs after the first intake of SLITone^{PLUS}; AEs documented in the diary; Serious Adverse Events (SAEs).

Statistical Methods
The following analysis sets were used:
- Full analysis set (FAS)
- Per protocol set (PP)
- Safety set (SS).

The aim was to demonstrate a non-inferior change from baseline in IgE-blocking factor in treatment Group V (vestibular) as compared to Group S (sublingual). The tests should be carried out one-tailed at a 2.5% level in the pre-specified order after 36, 24, 12, 8, and 4 weeks of treatment (non-inferiority margin: $\delta = -0.075$).

In the FAS, the primary endpoint was determined after imputing missing visits by means of **L**ast **O**bservation **C**arried **F**orward (i.e. by using the individually last measurement upon treatment – the so-called 'post treatment' value – as outcome). The further tests after 36, 24, 12, 8, 4 weeks are based on **O**bserved **C**ases.
The trial outcome should be classified as successful if a significant non-inferiority would be demonstrated on step 1 (post treatment) of the ordered test.
In case of successful trial outcome, tests of superiority of Group V vs. Group S should be carried out one-tailed at the level 2.5% at each control visit.

Demography of Trial Population

Parameter		Sublingual	Vestibular	All subjects
Number of subjects		38	33	71
Age [years]	mean (SD)	39.9 (12.6)	40.0 (10.6)	40.0 (11.6)
Gender	male	47.4%	42.4%	45.1%
	female	52.6%	57.6%	54.9%
Body height [cm]	mean (SD)	175 (10)	172 (9)	174 (10)
Body weight [kg]	mean (SD)	79 (21)	73 (16)	76 (19)
BMI [kg/m^2]	mean (SD)	25.5 (5.3)	24.4 (4.1)	25.0 (4.8)
Caucasian	mean (SD)	97.4%	93.9%	95.8%
Duration of rhinoconjunctivitis [years]				
	median	17	12	15
Bronchial asthma		31.6%	30.3%	31.0%
Specific immunotherapy in the history		28.9%	33.3%	31.0%

Pharmacodynamic Results
Except for Week 24, higher IgE-blocking factors against *Betula verrucosa* were seen after vestibular administration (V) compared with the sublingual route (S). The lower limits of the 95% confidence interval of the difference V – S were ≥ –0.075 except for Week 24. Therefore, non-inferiority could be concluded post treatment and at Week 36 taking into account the prespecified order of tests.
Estimating the type I error according to Bonferroni-Holm, multiple non-inferiority could be derived at all control visits except for Week 24. Superiority of V vs. S could be shown only at Week 4.
The repeated measurement analysis of $\ln(IgG_4)$ showed a slightly higher level upon V compared with S especially up to Week 12. The treatment differences concerning IgE were not relevant.

Safety Results

In the entire treatment phase (S vs. V: 84.2% vs. 84.8%), within 30 minutes after first intake (42.1% vs. 48.5%), on the entire day of first intake (65.8% vs. 60.6%), and with respect to local reactions related to the administration route (57.9% vs. 54.5%) no statistically significant differences in the incidences of AE were obtained. A slight but also insignificant tendency in favour of V was observed for pharyngeal oedema with N=6 upon sublingual and N=2 upon vestibular administration.

Taking into account the multiple occurrence of local reactions in the course of treatment, the comparison of the administration routes was performed by means of the proportion of days with specific events; the treatment differences in favour of V were not significant:

Adverse events		Sublingual	Vestibular	p-value
All events related to the administration route				
	raw data (U test)	12.6%	6.9%	0.5756
	GEE (Z value)	11.3%	6.9%	0.3468
Pharyngeal oedema	raw data (U test)	3.8%	0.4%	0.1966
	GEE (Z value)	1.7%	0.4%	0.2073

% of treatment days

GEE = Generalised estimating equations

Four subjects discontinued the trial due to adverse events possibly related to the trial medication: pharyngeal oedema + dysphagia (S), oedema mouth + mouth injury + conjunctivitis allergic + rhinorrhoea (V), asthma + dyspnoea (V), and vertigo (V), respectively.

Serious adverse events were not observed in this trial.

No treatment differences were observed for vital signs and physical examinations.

In both trial groups, the tolerability of SLITone^{PLUS} Birch was assessed as good to very good in approximately 90% of subjects.

Conclusions

- The primary aim of this randomised clinical trial was to demonstrate non-inferiority of vestibular (V) versus sublingual (S) administration of SLITone^{PLUS} Birch with respect to changes in IgE-blocking factor after 36 (in hierarchical order: 24, 12, 8, 4) weeks of treatment.
- Significant ($p<0.025$) non-inferiority could be shown post treatment (i.e. after 36 weeks of treatment where missing visits are imputed by means of **L**ast **O**bservation **C**arried **F**orward) and at Week 36 for **O**bserved **C**ases. Therefore, a successful trial outcome was achieved.
- Using the principle of α-adaptation according to Bonferroni-Holm, significant ($p<0.025$) non-inferiority could also be demonstrated after 4, 8, and 12 weeks of treatment.
- In all, a significant ($p<0.025$) non-inferiority of V versus S could be shown during the entire treatment phase except for Week 24 ($p=0.0504$).
- Superiority of V versus S with regard to changes from baseline in IgE-blocking factor was observed after 4 weeks only.
- Secondary endpoints were
  - the comparison of V and S with regard to changes from baseline in spec. IgG_4 against *Betula verrucosa*
  - the comparison of V and S with regard to changes from baseline in spec. IgE against *Betula verrucosa*
  - the comparison of V and S with regard to the incidences of the following local reactions: oral pruritus, oedema mouth, oropharyngeal swelling, pharyngeal oedema, swollen tongue, glossodynia.
- Higher levels of IgG_4 upon V were determined especially up to Week 12 (maximum 41.8%), but the treatment differences were not statistically significant. A higher level of IgE upon V remained statistically irrelevant (maximum 25.1%).
- No marked treatment differences were observed with respect to incidences of adverse events. Regarding adverse events related to the administration route, tendencies in favour of V (especially concerning pharyngeal oedema) remained statistically insignificant. However, in the most common Preferred Terms, (insignificant) tendencies in favour of vestibular administration were observed (especially paraesthesia oral, pharyngeal oedema, lip swelling, ear pruritus).
- Four subjects discontinued the trial due to adverse events possibly related to sublingual (N=1) or vestibular (N=3) administration of the IMP.

Conclusions *[cont.]* ▪ Serious adverse events were not reported. ▪ No treatment differences were observed for vital signs and physical examinations. ▪ In both trial groups, the tolerability of SLITone^{PLUS} Birch was assessed as good to very good in approximately 90% of subjects.
Date of the Report 11 January 2012
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