Efficacy of a 3-week subcutaneous immunotherapy course in patients with grass pollen-induced rhinoconjunctivitis: results of a phase-III study

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INTRODUCTION

Subcutaneous allergen immunotherapy (AIT) is safe and efficacious for the treatment of grass pollen rhinoconjunctivitis. Two major issues with current immunotherapy are the long-term treatment schedule and poor adherence (Calderon et al., 2007). A novel AIT using Lolium perenne peptides (LPP), based on highly purified allergen fragments from natural sources, has been developed for a 3-week treatment course for grass pollen rhinoconjunctivitis (gpASIT+, ASIT biotech sa). This study investigated the safety and tolerability of LPP administered prior to, and the clinical efficacy of LPP during natural exposure to grass pollen.

AIM

The primary objective

To demonstrate the clinical efficacy of LPP during the peak of the grass pollen season following subcutaneous administration to patients suffering from grass pollen rhinoconjunctivits with and without asthma.

The secondary objectives

- To assess individual symptom and medication scores over the peak and entire pollen season after treatment with LPP compared to placebo,
- To assess changes in allergic reactivity to Conjunctival Provocation Test (CPT) after treatment with LPP compared to placebo,
- To assess the Quality-of-Life of patients after treatment with LPP compared to placebo
- To assess the safety and clinical tolerability of LPP treatment.

The exploratory objective (in a subgroup of patients)

To assess the impact of LPP treatment on the immunological status of treated patients in comparison with placebo.

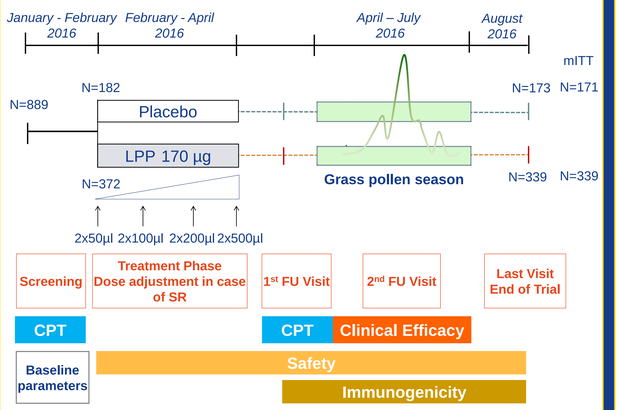
→ Presentation in LB OAS 5 – 21st June 2017 – 10:30 – Dr M Shamji

METHOD

- Randomised, double-blind, placebo controlled study
- 6 EU countries (Belgium, Czech Republic, France, Germany, Italy, Spain)
- 57 active sites

- The primary endpoint was the reduction - in the LPP treated group compared to the placebo group - of the Combined Symptom and Medication Score (CSMS) taking into account the daily Rhinoconjunctivitis Total Symptom Score (RTSS) and the daily Rescue Medication Score (RMS) (Pfaar et al., 2014)

- Secondary endpoint: Subscores over Pollen peak and entire pollen season



RESULTS

Demography and allergy diagnosis

	Placebo N=182	LPP N=372
Demography		
Age, mean ± SD (years)	34.1 ± 11.6	33.6 ± 11.1
Male/female (%)	57.7 / 42.3	51.6 / 48.4
Grass Pollen allergy		
Disease duration, mean ± SD (years)	13.7 ± 10.7	14.5 ± 11.0
Skin Prick Test, mean ± SD (mm)	8.3 ± 3.8	8.2 ± 3.3
Grass pollen-specific IgE level, mean ± SD (kU/L)	27.8 ± 29.8	27.6 ± 29.4
Asthma		
Patients with controlled asthma	39 (21.4 %)	95 (25.5%)

→ Patients baseline data were well balanced after randomization

Combined Symptom and Medication Score

	Placebo			LPP			Difference versus Placebo		
	N	Mean	SD	N	Mean	SD	Abs diff	Rel diff	P value*
Peak period	136	1.475	1.049	264	1.247	0.972	-0.228	-15.5%	0.041
Entire season	95	1.189	0.856	201	0.976	0.810	-0.213	-17.9%	0.029

Abs diff: absolute difference, Rel diff: relative difference. *Mann-Whitney test

* No normal distribution of the CSMS data, even after root square transformation. In this context, non parametric tests appeared to be the most reliable testing.

Subscores over the peak period

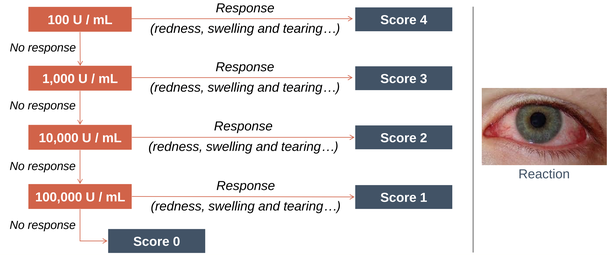
	Placebo			LPP			Difference versus Placebo		
	N	Mean	SD	N	Mean	SD	Abs Diff	Rel Diff	P value*
RTSS	150	4.498	3.513	284	3.665	3.169	-0.833	-18.5%	0.013
RMS	108	0.698	0.62	222	0.594	0.595	-0.104	-14.9%	0.152
NSS	156	3.318	2.502	289	2.704	2.335	-0.614	-18.5%	0.007
ESS	150	1.222	1.215	287	0.974	1.093	-0.248	-20.3%	0.046
Well days (%)	102	33.2	37.1	208	40.8	36.1	7.6	23.0%	0.044
LSS	32	0,964	1,641	67	0,517	0,899	-0,447	-46,4%	nd

NSS : Nasal Symptom Score; ESS Eye Symptom Score; LSS: Lung Symptom Score (only in asthmatic patients)
Abs diff: absolute difference, Rel diff: relative difference. *Mann-Whitney test

- The secondary endpoints support the primary endpoint analysis
- A mean RMS of 0.698 during peak pollen period in the placebo group suggests an overall low disease burden

Conjunctival Provocation Test

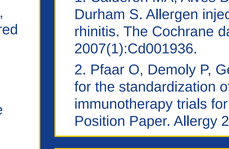
- Test performed before and after the treatment
- 4 different allergen concentrations used: 100; 1,000; 10,000 and 100,000 U/mL
- Measurement on a 5-point scale



Reaction

CPT outcome

Chi square Test



CSMS reduction according to CPT reactivity at baseline (post-hoc analysis)

Peak pollen

CPT score at baseline	Placebo			LPP			Difference versus Placebo		
	N	Mean	SD	n	Mean	SD	Abs diff	Rel diff	P value*
UNK	16	1.802	1.063	28	1.454	1.053	-0.348	-19.3%	nd
2	53	1.362	1.063	100	1.261	0.946	-0.101	-7.4%	nd
3	46	1.494	1.002	83	1.214	0.999	-0.28	-18.7%	nd
4	21	1.474	1.128	53	1.16	0.943	-0.314	-21.3%	nd
3&4	67	1.487	1.034	136	1.193	0.974	-0.294	-19.8%	0.051
All patients	136	1.475	1.049	264	1.247	0.972	-0.228	-15.5%	0.041

Abs diff: absolute difference, Rel diff: relative difference. *Mann-Whitney test

Entire pollen season

CPT score at baseline	Placebo			LPP			Difference versus Placebo		
	n	Mean	SD	n	Mean	SD	Abs diff	Rel diff	P value*
UNK	14	1.457	0.878	21	1.237	0.716	-0.22	-15.1%	nd
2	35	1.058	0.807	72	0.997	0.918	-0.061	-5.8%	nd
3	30	1.176	0.933	62	0.909	0.721	-0.267	-22.7%	nd
4	16	1.264	0.806	46	0.917	0.783	-0.347	-27.5%	nd
3&4	46	1.207	0.883	108	0.912	0.745	-0.295	-24.4%	0.047
All patients	95	1.189	0.856	201	0.976	0.81	-0.213	-17.9%	0.029

Abs diff: absolute difference, Rel diff: relative difference. *Mann-Whitney test

In LPP treated patients, the CSMS reduction during the peak pollen period and the entire pollen season (compared to placebo) is larger in the subgroup of patients with CPT score of 3&4 at baseline, than in those with a CPT score of 2. The difference versus placebo in the subgroup of CPT score 3 and 4 is significant.

RQLQ : Quality of life data are in line with efficacy data.

SAFETY

Target dose

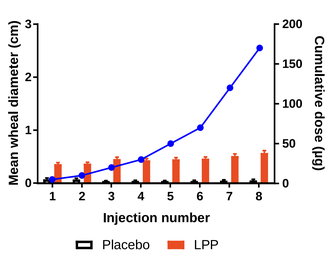
	Placebo N=177	LPP N=368
Patients who received 170 µg, n (%)	171 (96,61%)	329 (89,40%)
Reached in 8 injections	168 (98,25%)	312 (94,83%)
Reached in >8 injections	3 (1,75%)	17 (5,17%)

System Reaction grading

WAO classification	Placebo N=177		LPP N=368	
	Events	Pat. (%)	Events	Pat. (%)
All grades	10	9 (5.1%)	117	75 (20.4%)
Grade 1	9	8 (4.5%)	94	61 (16.6%)
Grade 2	1	1 (0.6%)	21	19 (5.2%)
Grade 3	0	0 (0%)	1	1 (0.3%)
Grade 4	0	0 (0%)	1	1 (0.3%)

- No evidence of dose-relationship (5-50µg)
- Grade 3 and 4 events occurred after 5µg injection, ≤ 30 minutes
- All events but 1 were considered 'related'; all patients recovered
- 3 'serious' events were reported (occured after first injection, within 30 minutes):
  - 1 grade 4 (moderate): serious hypotension requiring medication (Clemastin (2 ml, IV), Prednison (500 mg, IV and adrenaline (100 mg IV), day-care hospitalisation, patient recovered the same day.
  - 1 grade 3 (severe): bronchospasm with uvula oedema and systemic urticaria, handled without adrenaline nor oxygen, patient recovered the same day)
  - 1 grade 2 (moderate): generalised urticaria and bronchospasm

Local Reactions



Mean wheal diameters 30 minutes after injection were less than 0.6 cm and no increase was observed with dose increase. The blue line shows the cumulative dose at the respective injection.

CONCLUSIONS

- LPP consistently improved clinical symptoms and reduced medication use (CSMS) of allergic rhinitis patients with 15.5% (peak pollen period, p=0.04, imputation 1) to 17.9 % (entire pollen season, p=0.03) compared to placebo
- Clinical provocation testing responses observed further support the clinical efficacy findings
  - In a subgroup of patients with the highest CPT reactivity at baseline (grade 3 and 4), this improvement (over placebo) reached or exceeded 20% (20% over the peak, 24% over the entire season; post-hoc analysis)
  - CPT reactivity at baseline was predictive of later clinical response
- Improvement in Quality of Life was in line with efficacy endpoints
- LPP treatment was overall well tolerated yielding mostly mild adverse reactions. The more severe system allergic reaction occurred upon the first injection. No new or unexpected safety finding was observed.
- The clinical efficacy of LPP is supported by the observed immunogenicity data → see Oral presentation Dr M Shamji on Wednesday 21/06 room 10:00)

These positive results confirm the efficacy and safety of short course treatment of adjuvant free peptide preparation in this patient population. CPT at baseline may be used to select the patients who will benefit most.

REFERENCES

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