2004-02-03

Final Report

LUIPAS

long-term examination

Supplement to the final report LUI-01-00 of March, 27, 2003

LUIVAC®/ PASPAT® oral Treatment under Daily Life Conditions in Patients with Recurrent Respiratory Tract Infections including Obstructive Pulmonary Diseases

Multinational Post-Authorisation Study in

Austria, Czech Republic, Dominican Republic, Latvia, Poland, Portugal, Slovakia, Switzerland, Venezuela,

Contents:

1. List of abbreviations

ADR	Adverse Drug Reaction
BMI	Body Mass Index
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
DSCG	Disodium Cromoglycate
ENT	Specialist for Ears, Nose and Throat
GP	General Practitioner
LSO	Local Safety Officer
PAC	Protocol Approval Committee
PAS	Post-Authorisation Study
PhVWP	Pharmacovigilance Working Party
RTI	Respiratory Tract- Infection
SAS®	Statistical Analysis Software
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics

2. Directory

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3. Summary

aim of the PAS: assessment of the long-term influence of therapy with LUIVAC® / PASPAT® oral on frequency, intensity, duration of recurrent respiratory tract infections (RTI), absence days from work/kindergarten and specific concomitant medication in patients who had received the therapy the year before, number of patients with necessity for further treatment, physician's judgement for efficacy.

observation design: open, multicentre, multinational, observational study

patients: 1265 of 1615 patients with recurrent upper and lower respiratory infections including patients who additionally suffered from obstructive pulmonary diseases were examined approximately one year after the treatment with LUIVAC® /PASPAT® oral. Of those 1258 could be evaluated

centres: 128 of 181 ENTs, GPs, paediatricians, immunologists, pulmonologists, allergists and internists in total, distributed to Austria, Czech Republic, Latvia, Poland, Portugal, Slovakia, Switzerland, Venezuela/Dominican Republic provided one year data of patients treated with LUIVAC® /PASPAT®

drug: LUIVAC® /PASPAT® oral

duration of the PAS: treatment period August 2000 until December 2001
treatment free long-term observation until November 2002

frequency of examinations: Visit V4 approximately one year after the treatment of LUIVAC® /PASPAT® oral, three visits were recommended at the beginning of the treatment V1, before the second intake cycle V2 and after treatment V3

observation criteria:

- specification of respiratory tract infections
- number, intensity, duration of respiratory tract infections in the treatment free period
- number of absence days in the treatment free period
- specific concomitant medication
- further treatment with LUIVAC® /PASPAT® oral
- doctor's judgement for long-term efficacy

duration of treatment: two intake cycles with LUIVAC® /PASPAT® oral of 4-weeks duration each, according to the SPC

results: After one year 128 of 181 centres examined 1265 of 1615 patients originally included in the post-authorisation study (LUIPAS). 1258 patients who attended all required visits could be evaluated. It has to be mentioned that the results of the long-term observation are only comparable with limitation to those achieved during and after the treatment cycles du to different duration of the periods. The number of patients without infections at the time of visit 4 stayed fairly unchanged since the recording at visit 3, corresponding with an increase of approximately 62% compared to the beginning at visit 1. The intensity of such infections was mild in 67% of the patients and moderate in 31%. The number of patients with infections during the period V1-V3 compared to that of V3-V4 stayed fairly constant, but the frequency of infections decreased from 14% to 0.6% for more than eight infections, from 51% to 8% for 5-7, increased from 34% to 72% for less then four infections and 20% had no infections any more. The concomitant medication was reduced by 52%, the number of absence days from work also by 48% and from school/kindergarten by 56%.
The necessity for further treatment with LUIVAC® /PASPAT® oral was confirmed for 49% of the re-examined patients.
The long-term efficacy stated by the treating doctors was very good/good in 91% and insufficient only in 2 %.

ADR: n.a. due to treatment free observation period

Summary – continued

128 of originally 181 centres (ENTs, GPs, paediatricians, immunologists, pulmonologists) which included 1615 patients with recurrent respiratory tract infections were able to re-examine 1265 of them approximately one year after the intake of LUIVAC® /PASPAT® oral as recorded in the documents of the post-authorisation study LUIPAS. The data of 1258 patients who attended the control visits 2 - 4 could be evaluated and compared.
The underlying question was to investigate the long-term efficacy of LUIVAC® /PASPAT® oral regarding the number of patients who experienced any RTI within these twelve months, the

number, intensity and duration of such RTIs, the number of absence days from work, school or kindergarten, possible concomitant medication at time of examination, possible necessity for another treatment with LUIVAC® /PASPAT® oral and the doctor's judgement for efficacy of the treatment.

18% of the patients in Venezuela as minimum and 99.5% of the patients in Slovakia suffering from recurrent respiratory tract infections who were observed during the two treatment cycles with LUIVAC® /PASPAT® oral attended another visit approximately one year later. The percentage of long-term observed patients in all other countries was within this range.

There was a clear decrease of the frequency of infections during the last observation period between visit V3 and V4 compared to the last twelve months before the beginning of the treatment with LUIVAC® /PASPAT® oral. Patients who did not suffer from any infection after been treated with LUIVAC® /PASPAT® oral were 20% compared to 0% before and less than 4 infections in 72 % in the same period compared to 34% before. Five to seven and more than eight infections occurred only in 9% compared to 66% before.

Acute infections at the time of the control visit were unambiguously reduced compared to the beginning of the observation. 86% of the patients were without any infection. The intensity of infection was only asked generally and not assigned to each diagnose.

Also the number of patients taking concomitant medication compared to that of the first observation period decreased by 52%. The reduction for antibiotics was 70% and for steroids 49%. The mean number of absence days from work reduced by 48%, from school or kindergarten by 56%.

In 51 % of the patients there was no necessity for further treatment with LUIVAC® /PASPAT® oral. The statement for efficacy related to the long-term efficiency of LUIVAC® /PASPAT® oral was 91% for very good/good, only 7% had a satisfactory result and 2% an insufficiency. The comparison of efficacy assessment between the statement at visit V3 and V4 remained nearly unchanged.

4. Introduction

Basing on the discussion about the sometimes exaggerated and unnecessary use of antibiotics for many indications related to respiratory tract infections, the search for alternative treatments is required. LUIVAC®/Paspat® oral an immunotherapeutical agent, is a lysate of seven bacteria commonly involved in respiratory tract infections: *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus mitis, Staphylococcus aureus, Haemophilus influenzae, Branhamella (Moraxella) catarrhalis and Klebsiella pneumoniae.* It is proved in clinical trials in more than 6000 patients as preventive and supportive measure for patients with recurrent respiratory tract infections.

The mode of action of LUIVAC®/Paspat® oral is based on the stimulation of the common mucosa-associated lymphoid tissue (MALT). The absorption of the antigens in the small intestine is followed by the priming of its lymphoid tissue. The primed immune cells in the Peyer's patches migrate from the small intestine via the lymphatic system and the blood circulation to even distant mucosal tissues as the respiratory tract. This procedure is called homing. In the target organs they are responsible for an increase in the specific immunity by an enhancement of the antigen-specific secretory immuno-globulin A response to local challenge [1] - [4]

Since the approval by the 'Paul Ehrlich Institut für Sera und Impfstoffe' in Germany for the treatment of recurrent respiratory tract infections, 1992, LUIVAC®/Paspat® oral is available in more than 25 countries world-wide.

Between August 2000 until December 2001 1615 patients suffering from recurrent respiratory tract infections and treated with LUIVAC®/Paspat® oral were observed in a post-authorisation study running in nine countries world-wide. A decrease of the number of patients with infections by 10% and the number of infections by 18% could be seen after the treatment cycle comprising two periods of tablet intake according to the instructions for use. The duration and intensity of the infections were reduced, also the intake of concomitant medication [5].

As it is of interest to get knowledge about the long-term efficacy of an immuno modulating therapy we asked the participating investigators for more information about the involved patients approximately one year after the second treatment period.

5. Objectives of the Observation

- assessment of the influence of therapy with LUIVAC® /PASPAT® oral on frequency, intensity and duration of respiratory tract infections in patients with recurrent respiratory tract infections under daily life conditions in consideration of patients who additionally suffer from obstructive pulmonary diseases. Comparison of the frequency, intensity and duration of respiratory tract infections before and after the treatment LUIVAC® /PASPAT® oral.
- comparison of absence days from kindergarten/school / work/household during and after the treatment LUIVAC® /PASPAT® oral.
- comparison of specific concomitant therapy during and after the treatment LUIVAC® /PASPAT® oral.
- number of patients with necessity for further treatment with LUIVAC® /PASPAT® oral
- physician's judgement for efficacy and tolerability

6. Investigational plan

The investigators of the centres who had contributed the data of patients in the PAS LUI-01-00 (LUIPAS) were asked to answer approximately one year after the participation of those the same questionnaire as during the treatment cycles. This investigation was on an optional basis.

6.1. Investigational centres

128 of 181 centres of GPs, internists, ENTs, allergists, paediatricians, pulmonologists, or hospital services [Table 7] participated in the long-term observation:

9 centres in Austria,

23 in the Czech Republic,

25 in Poland,

31 in Portugal,

15 in the Slovak Republic,

7 in Latvia,

16 in Switzerland,

1 in Venezuela and

1 in the Dominican Republic.

6.2. Observed population

1265 patients attended the visit after one year. 1258 attending all visits could be evaluated [Table 5,Table 9].

6.2.1. Inclusion criteria

Only data of patients treated with LUIVAC® /PASPAT® oral the year before could be recorded

6.2.2. Exclusion criteria

none

6.3. Ethics / Patient information

As described in the observational plan of LUI-01-00

6.4. Medication

As described in the observational plan of LUI-01-00

6.4.1. Measures for treatment compliance

n.a

6.4.2. Prior and concomitant therapy

Inquiry about the intake of beta-2 agonists/theophyllin, antibiotics, steroids, anti-inflammatory agents/DSCG or symptomatic therapy since the end of the treatment with LUIVAC® /PASPAT® oral.

6.5. Schedule

Examination of the patients approximately one year after treatment.

6.6. Data Management

As described in the observational plan of LUI-01-00

6.7. Statistical plan and documentation of statistical methods

The data were analysed in a descriptive way. Measurements for localisation (mean, median) and dispersion (standard deviation, range) were calculated for interval scaled variables, whereas ordinarily and categorically scaled variables should be analysed by calculation of frequencies.

7. Observed patients

7.1. Number of patients entered and followed-up

1265 of 1615 patients (78%) were examined one year after the second treatment period. The data of 1258 could be evaluated as these patients attended the visits V2, V3, V4 which was essential for the comparison of items to achieve the objectives of the observation [Table 5,Table 6,Table 7,Table 8].

7.2. Demographic and other baseline characteristics

These parameter regarding, age, gender, BMI were only respected in the evaluation of the population included in the treatment period, but not in the investigation after one year.

7.3. Compliance

n.a.

8. Efficacy Results

Similar as after the termination of the second treatment period at visit 3, the doctors stated the efficacy after one year still with very good in 60% of the patients, good in 31%, satisfactory in 7% and insufficient in 2%.

In 6% of the patients who had only satisfactory or insufficient efficacy the year before, the doctors reported at visit V4 a good or very good efficacy, however the same percentage was stated for patients with very good/good efficacy in the last year who turned down to satisfactory/insufficient efficacy now [Table 24,Table 25].

The mean number of absence days per month for patients with an occupation decreased from 0.66 in the period V1-V3 to 0.34 in the period V3-V4. For children the mean number of absence days from school or kindergarten in the same periods decreased from 1.72 to 0.76 [Table 23].

The percentage of patients taking any concomitant medication decreased from 81% in the period V1-V3 to 39%. The reduction of use of antibiotics from period V1-V3 to V3-V4 by 70% was most impressive, but also the reduction of steroids by 49% was remarkable [Table 16,Table 17,Table 18,Table 19,Table 20,Table 21,Table 22].

There was necessity for another treatment with LUIVAC® /PASPAT® oral in 49% of the examined patients, and none in 51% [Table 26].

8.1. Changes in clinical signs and symptoms

The number of patients without an acute infection at the time of examination increased from 53% at visit 1 to 86% at visit 4 [Table 10].

The number of patients who experienced infections during the period V1-V2 (53%) was almost the same as in period V3-V4 (55%). However, it has to be considered that the duration of the observed periods V1-V2 (8 weeks) and V3-V4 (app. one year) differ and thus can only be compared with limitation.

The comparison of the frequency of infections in the year before and the year after the treatment with LUIVAC® /PASPAT® oral shows a decrease for more than 8 infections from 14% to 0.6%, for 5-7 infections from 51% to 8%, an increase for less than 4 infections from 34% to 72% and 20% of the patients who had no infection at all [Table 14]. These findings exceed the expectations basing on the results from the observation period V1-V3, explained in the final report LUIPAS (27.03.02).

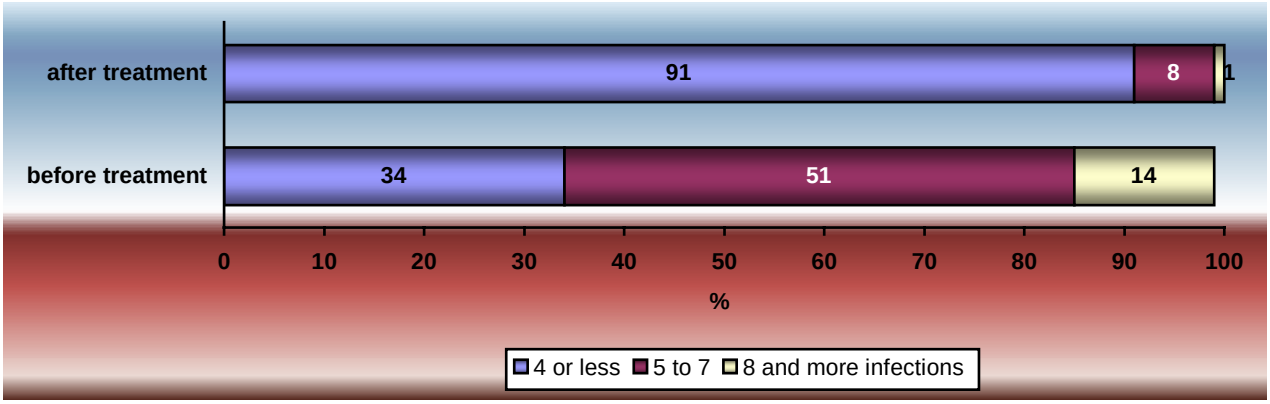

Figure 1 Frequency of infections per patient stratified by number of infections in the year before and approximately one year after the treatment

8.2. Subgroup analysis

The decrease of the frequency of concomitant medication was comparable in the countries participating in this observation [Table 16 - Table 21].

The number of patients with infections at visit V4 was only clearly reduced in Portugal (73% to 41%), slightly in Switzerland (54% to 48%), increased in Poland from 53% to 75% and in the Slovak Republic from 47% to 55%. All others stayed fairly the same [Table 13].

8.3. Efficacy conclusions

The number of patients with infections regarding the present status at the time of the last visit (V4) was clearly reduced, in comparison to the number of patients at visit V1 [Table 10].
The number of patients with infections stratified by duration remained fairly constant for the period V1-V2 and V3-V4 [Table 15]. However the frequency of infections in the year after the treatment period decreased clearly compared to the recorded number of infections the year before the treatment with LUIVAC® / PASPAT® oral [Table 14].

The intensity of infections before the beginning of the treatment at visit V1 was not classified to mild/moderate/severe. During the observation the intensity of infections was recorded in relation to the number and duration of infections. The duration of the observed periods however was only comparable for V1-V2 and V2-V3 whereas the period V3-V4 was much longer. Therefore, the intensity score comprising the intensity of infections related to the number of infections could not be used for the overall comparison of the observed periods. [Table 11], however the situation at visit V4 shows that 97% of the patients suffered only from respiratory infections of mild (67%) to moderate (31%) intensity.

The reduction of the number of patients taking concomitant medication [Table 22] may refer to the reduced frequency of the infections resulting from the treatment with LUIVAC® / PASPAT® oral. The assignment of concomitant medication to a certain kind of respiratory tract infection was not subject of the investigation after one year.

Also the number of absence days of work, school or kindergarten was remarkably reduced and gives reason to assume a long-term efficacy of the treatment with LUIVAC® /PASPAT® oral.

9. Safety evaluation

n.a.

9.1.1. Status of all patients completed, on/off treatment, deceased, lost to follow up

Of 1615 patients included at visit 1, 1265 were recorded for the last visit V4, of those 1258 attended the visits before, after and approximately one year after treatment and were thus appropriate for the evaluation.

9.1.2. Reasons for stopping the treatment

n.a

9.2. Adverse Drug Reactions

n.a.

9.3. Global assessment for tolerability

n.a.

9.4. Clinical laboratory evaluation

n.a.

9.5. Vital signs, physical findings and other observations related to safety

n.a

9.6. Safety conclusions

n.a.

10. Discussion and overall conclusions

The influence of LUIVAC® /PASPAT® oral on the number, intensity and duration of respiratory tract infections has mostly been observed during the treatment periods within clinical or observational studies, but the experience regarding those parameter on the long term efficacy has never been described within a post-authorisation study.

Subsequent to the post-authorisation study LUIPAS conducted between August 2000 and December 2001, where patients with recurrent respiratory tract infections were treated with LUIVAC® /PASPAT® oral for two treatment periods, the participating investigators were asked to examine the included patients again approximately one year later until November 2002, and to record number, intensity and duration of respiratory tract infections occurred since visit V3 to investigate the long-term efficacy of the product under all days conditions.

Though it could only be asked for another attendance at the examination approximately one year after the LUIPAS observation period of sixteen weeks, V1-V3, the numerous participation at visit V4 was surprising and might be explained by the satisfaction with the efficacy of the medication.

For all investigations performed at visit V4, it has to be respected that the different duration of the observed periods allows only limited conclusions and promising results should stimulate for further controlled trials.

Regarding the number of patients with infections the results in general remain fairly constant for all observed periods, but the extended duration of the period V3-V4 compared to that of V1-V2 and V3-V4 increases the likelihood to get an infection and therefore a statement for any comparison should be made with caution.

The comparison of the frequency of infections in the year before the treatment with LUIVAC® /PASPAT® oral and the year after showed a clear reduction of the number of infections which leads to the conclusion of the long-term effect of the medication. Within these periods a comparison can be drawn, as the requested space of time was always one year.

Remarkable is the reduction of concomitant medication by 52% as antibiotics, anti inflammatory agents, beta-agonists, steroids or symptomatic therapy. This observation is confirmed by the reduction of the percentage of patients taking concomitant medication from 81% during treatment to 39 % in the year after treatment with LUIVAC® /PASPAT® oral and also by the fact of a clear reduction of absence days from work, kindergarten or school. It might be considered to confirm these findings in a clinical trial as a comparable study so far exists only in children.

Possible reasons for the reduction of the number of patients with infections at visit V 4 in some countries and the increase in other has to be scrutinised and discussed with the concerned partners.
In a post-authorisation study there are no obligations for doctors and patients to perform or to participate in a visit at the study centre. Therefore it can be assumed for the long-term investigation that mainly doctors with high interest in the product or patients convinced by there experience with LUIVAC® /PASPAT® oral were motivated to participate in another visit after one year.

These results lead to the conclusion that the number of patients with infections, the frequency of infections in general, the number of absence days from work/school/kindergarten and the consumption of concomitant medication could be reduced by the treatment with LUIVAC® /PASPAT® oral. The duration of the infections stayed fairly stable between the observed periods. These facts in connection with the statement of the physicians for an excellent efficacy and safety confirm that LUIVAC® /PASPAT® oral is an important supportive treatments for recurrent respiratory tract infections.

11. Reference list

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13. Figures - contents

14. Tables - contents

Table 1 : Date first patient in study

first patient in
29/08/2000

Table 2 : Date last patient in study

last patient in
01/08/2001

Table 3 : Date first patient finished study (incl. V4)

first patient out
15/03/2001

Table 4 : Date last patient finished study (incl. V4)

last patient out
11/11/2002

Table 5 : Number of patients per visit

visit	no. of patients
V1	1615
V2	1577
V3	1584
V4	1265

Table 6 : Number of patients per visit and country

country	visit	no. of patients
Austria	V1	206
Austria	V2	201
Austria	V3	199
Austria	V4	39
Czech Repub.	V1	230
Czech Repub.	V2	230
Czech Repub.	V3	230
Czech Repub.	V4	224
Poland	V1	250
Poland	V2	250
Poland	V3	250
Poland	V4	242
Portugal	V1	167
Portugal	V2	167
Portugal	V3	167
Portugal	V4	133
Slovak Repub.	V1	225
Slovak Repub.	V2	225
Slovak Repub.	V3	225
Slovak Repub.	V4	224
Latvia	V1	353
Latvia	V2	335
Latvia	V3	353
Latvia	V4	331
Switzerland	V1	124
Switzerland	V2	116
Switzerland	V3	103
Switzerland	V4	56
Venezuela	V1	50
Venezuela	V2	43
Venezuela	V3	47
Venezuela	V4	9
Dom. Repub.	V1	10
Dom. Repub.	V2	10
Dom. Repub.	V3	10
Dom. Repub.	V4	7

Table 7 : Number of centres per country and visit

country	visit	no. of centres
Austria	V1	40
Austria	V2	40
Austria	V3	40
Austria	V4	9
Czech Repub.	V1	23
Czech Repub.	V2	23
Czech Repub.	V3	23
Czech Repub.	V4	23
Poland	V1	25
Poland	V2	25
Poland	V3	25
Poland	V4	25
Portugal	V1	36
Portugal	V2	36
Portugal	V3	36
Portugal	V4	31
Slovak Repub.	V1	15
Slovak Repub.	V2	15
Slovak Repub.	V3	15
Slovak Repub.	V4	15
Latvia	V1	7
Latvia	V2	7
Latvia	V3	7
Latvia	V4	7
Switzerland	V1	29
Switzerland	V2	29
Switzerland	V3	28
Switzerland	V4	16
Venezuela	V1	5
Venezuela	V2	5
Venezuela	V3	5
Venezuela	V4	1
Dom. Repub.	V1	1
Dom. Repub.	V2	1
Dom. Repub.	V3	1
Dom. Repub.	V4	1

Table 8 : Number of patients per country and centre with V4

country	centre no.	no. of patients
Austria	1	5
Austria	7	5
Austria	10	1
Austria	21	5
Austria	30	2
Austria	34	8
Austria	37	4
Austria	38	5
Austria	39	4
Czech Repub.	1	10
Czech Repub.	2	10
Czech Repub.	3	10
Czech Repub.	4	10
Czech Repub.	5	10
Czech Repub.	6	9
Czech Repub.	7	7
Czech Repub.	8	10
Czech Repub.	9	10
Czech Repub.	10	10
Czech Repub.	11	10
Czech Repub.	12	8
Czech Repub.	13	10
Czech Repub.	14	10
Czech Repub.	15	10
Czech Repub.	16	10
Czech Repub.	17	10
Czech Repub.	18	10
Czech Repub.	19	10
Czech Repub.	20	10
Czech Repub.	21	10
Czech Repub.	22	10
Czech Repub.	23	10
Poland	1	10
Poland	2	10
Poland	3	10
Poland	4	10
Poland	5	8
Poland	6	11
Poland	7	10
Poland	8	10
Poland	9	10
Poland	10	8
Poland	11	10
Poland	12	9
Poland	13	10
Poland	14	10
Poland	15	10
Poland	16	9

-continued

Poland	17	10
Poland	18	10
Poland	19	10
Poland	20	10
Poland	21	10
Poland	22	7
Poland	23	10
Poland	24	10
Poland	25	10
Portugal	4	2
Portugal	5	2
Portugal	6	4
Portugal	7	4
Portugal	8	3
Portugal	9	5
Portugal	10	5
Portugal	11	4
Portugal	12	4
Portugal	13	4
Portugal	15	4
Portugal	17	2
Portugal	18	2
Portugal	19	3
Portugal	20	5
Portugal	21	5
Portugal	22	5
Portugal	26	5
Portugal	29	5
Portugal	32	5
Portugal	33	5
Portugal	34	5
Portugal	35	4
Portugal	36	5
Portugal	37	5
Portugal	38	10
Portugal	39	4
Portugal	40	5
Portugal	41	4
Portugal	42	3
Portugal	44	5
Slovak Repub.	1	15
Slovak Repub.	2	15
Slovak Repub.	3	15
Slovak Repub.	4	15
Slovak Repub.	5	15
Slovak Repub.	6	15
Slovak Repub.	7	15
Slovak Repub.	8	15
Slovak Repub.	9	15
Slovak Repub.	10	15
Slovak Repub.	11	15
Slovak Repub.	12	15

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Slovak Repub.	13	14
Slovak Repub.	14	12
Slovak Repub.	15	18
Latvia	1	101
Latvia	2	86
Latvia	3	41
Latvia	4	32
Latvia	5	27
Latvia	6	23
Latvia	7	21
Switzerland	1	5
Switzerland	9	1
Switzerland	10	3
Switzerland	11	5
Switzerland	13	2
Switzerland	14	2
Switzerland	21	5
Switzerland	26	5
Switzerland	27	5
Switzerland	31	5
Switzerland	32	4
Switzerland	43	5
Switzerland	46	2
Switzerland	49	3
Switzerland	51	3
Switzerland	59	1
Venezuela	2	9
Dom. Repub.	6	7

Table 9 : Number of patients with information at V2, V3 and V4

		n	%
V2, V3, V4 exist	no	357	22.1
	yes	1258	77.9

Table 10 : Present status

		visit							
		V1		V2		V3		V4	
		n	%	n	%	n	%	n	%
without infection	no	593	47.1	187	14.9	109	8.7	180	14.3
	yes	665	52.9	1071	85.1	1149	91.3	1078	85.7
upper resp. tract inf.	no	840	66.8	1109	88.2	1175	93.4	1143	90.9
	yes	418	33.2	149	11.8	83	6.6	115	9.1
lower resp. tract inf.	no	1074	85.4	1225	97.4	1236	98.3	1199	95.3
	yes	184	14.6	33	2.6	22	1.7	59	4.7
acute otitis media	no	1227	97.5	1252	99.5	1254	99.7	1246	99.0
	yes	31	2.5	6	0.5	4	0.3	12	1.0

Table 11 : Intensity of respiratory tract infection at V4

		n	%
intensity	missing	1	0.6
	mild	120	66.7
	moderate	55	30.6
	severe	4	2.2

(globally evaluated, not assigned to duration or specific infection)

Table 12: Number of patients with infections per period

		period					
		V1-V2		V2-V3		V3-V4	
		n	%	n	%	n	%
infection	no	594	47.2	729	57.9	565	44.9
	yes	664	52.8	529	42.1	693	55.1

Table 13 : Number of patients with infections stratified by country

country		period V1-V2 n	%	V2-V3 n	%	V3-V4 n	%
Austria	no	25	64.1	22	56.4	24	61.5
	yes	14	35.9	17	43.6	15	38.5
Czech Repub.	no	98	43.8	119	53.1	90	40.2
	yes	126	56.3	105	46.9	134	59.8
Dom. Repub.	no	1	14.3	5	71.4	7	100.0
	yes	6	85.7	2	28.6	.	.
Latvia	no	169	51.1	175	52.9	170	51.4
	yes	162	48.9	156	47.1	161	48.6
Poland	no	114	47.1	117	48.3	60	24.8
	yes	128	52.9	125	51.7	182	75.2
Portugal	no	36	27.1	108	81.2	78	58.6
	yes	97	72.9	25	18.8	55	41.4
Slovak Repub.	no	120	53.6	142	63.4	102	45.5
	yes	104	46.4	82	36.6	122	54.5
Switzerland	no	23	46.0	33	66.0	26	52.0
	yes	27	54.0	17	34.0	24	48.0
Venezuela	no	8	100.0	8	100.0	8	100.0

Table 14 : Frequency of infections per patient within the last 12 months and during observation

		n	%
frequency of infections within the last 12 months before the treatment	<= 4	432	34.3
	5-7	645	51.3
	> 8	181	14.4
frequency of infections during observation	0	247	19.6
	<= 4	905	71.9
	5-7	99	7.9
	> 8	7	0.6

Table 15 : Number of patients with infections per period stratified by duration

	V3_V4			
V1-V2	no infect	<= 7 days	8-14 days	> 14 days
no infect	311	192	76	15
<= 7 days	190	179	81	20
8-14 days	46	52	37	12
> 14 days	18	15	8	6

Table 16 : Comparison of frequency of concomitant medication by country and period - Beta 2-agonist

	V1-V3				V3-V4			
	no		yes		no		yes	
	n	%	n	%	n	%	n	%
country								
Austria	23	59.0	16	41.0	33	84.6	6	15.4
Czech Repub.	174	77.7	50	22.3	201	89.7	23	10.3
Poland	173	71.5	69	28.5	204	84.3	38	15.7
Portugal	109	82.0	24	18.0	126	94.7	7	5.3
Slovak Repub.	174	77.7	50	22.3	204	91.1	20	8.9
Latvia	285	86.1	46	13.9	309	93.4	22	6.6
Switzerland	38	76.0	12	24.0	45	90.0	5	10.0
Venezuela	7	87.5	1	12.5	8	100.0	.	.
Dom. Repub.	.	.	7	100.0	7	100.0	.	.
all countries	983	78.1	275	21.9	1137	90.4	121	9.6

Table 17 : Comparison of frequency of concomitant medication by country and period - Antibiotics

	V1-V3				V3-V4			
	no		yes		no		yes	
	n	%	n	%	n	%	n	%
country								
Austria	26	66.7	13	33.3	35	89.7	4	10.3
Czech Repub.	188	83.9	36	16.1	218	97.3	6	2.7
Poland	178	73.6	64	26.4	223	92.1	19	7.9
Portugal	71	53.4	62	46.6	129	97.0	4	3.0
Slovak Repub.	154	68.8	70	31.3	201	89.7	23	10.3
Latvia	228	68.9	103	31.1	284	85.8	47	14.2
Switzerland	33	66.0	17	34.0	45	90.0	5	10.0
Venezuela	5	62.5	3	37.5	8	100.0	.	.
Dom. Repub.	.	.	7	100.0	7	100.0	.	.
all countries	883	70.2	375	29.8	1150	91.4	108	8.6

Table 18 : Comparison of frequency of concomitant medication by country and visit - Antiinflammatory agents/DSCG

	V1-V3				V3-V4			
	no		yes		no		yes	
	n	%	n	%	n	%	n	%
country								
Austria	30	76.9	9	23.1	37	94.9	2	5.1
Czech Repub.	163	72.8	61	27.2	211	94.2	13	5.8
Poland	112	46.3	130	53.7	169	69.8	73	30.2
Portugal	81	60.9	52	39.1	125	94.0	8	6.0
Slovak Repub.	155	69.2	69	30.8	208	92.9	16	7.1
Latvia	278	84.0	53	16.0	314	94.9	17	5.1
Switzerland	38	76.0	12	24.0	46	92.0	4	8.0
Venezuela	7	87.5	1	12.5	8	100.0	.	.
Dom. Repub.	3	42.9	4	57.1	6	85.7	1	14.3
all countries	867	68.9	391	31.1	1124	89.3	134	10.7

Table 19 : Comparison of frequency of concomitant medication by country and visit - Symptomatic therapy

	V1-V3				V3-V4			
	no		yes		no		yes	
	n	%	n	%	n	%	n	%
country								
Austria	17	43.6	22	56.4	33	84.6	6	15.4
Czech Repub.	99	44.2	125	55.8	188	83.9	36	16.1
Poland	107	44.2	135	55.8	176	72.7	66	27.3
Portugal	78	58.6	55	41.4	117	88.0	16	12.0
Slovak Repub.	64	28.6	160	71.4	165	73.7	59	26.3
Latvia	84	25.4	247	74.6	217	65.6	114	34.4
Switzerland	33	66.0	17	34.0	42	84.0	8	16.0
Venezuela	3	37.5	5	62.5	8	100.0	.	.
Dom. Repub.	5	71.4	2	28.6	4	57.1	3	42.9
all countries	490	39.0	768	61.0	950	75.5	308	24.5

Table 20 : Comparison of frequency of concomitant medication by country and visit - Steroids

	V1-V3				V3-V4			
	no		yes		no		yes	
	n	%	n	%	n	%	n	%
country								
Austria	25	64.1	14	35.9	32	82.1	7	17.9
Czech Repub.	178	79.5	46	20.5	191	85.3	33	14.7
Poland	165	68.2	77	31.8	201	83.1	41	16.9
Portugal	120	90.2	13	9.8	129	97.0	4	3.0
Slovak Repub.	181	80.8	43	19.2	203	90.6	21	9.4
Latvia	306	92.4	25	7.6	321	97.0	10	3.0
Switzerland	35	70.0	15	30.0	45	90.0	5	10.0
Venezuela	7	87.5	1	12.5	8	100.0	.	.
Dom. Repub.	5	71.4	2	28.6	7	100.0	.	.
all countries	1022	81.2	236	18.8	1137	90.4	121	9.6

Table 21 : Comparison of frequency of concomitant medication by country and period

	V1-V3				V3-V4			
	no		yes		no		yes	
	n	%	n	%	n	%	n	%
country								
Austria	5	12.8	34	87.2	24	61.5	15	38.5
Czech Repub.	59	26.3	165	73.7	145	64.7	79	35.3
Poland	31	12.8	211	87.2	109	45.0	133	55.0
Portugal	31	23.3	102	76.7	105	78.9	28	21.1
Slovak Repub.	35	15.6	189	84.4	144	64.3	80	35.7
Latvia	63	19.0	268	81.0	199	60.1	132	39.9
Switzerland	12	24.0	38	76.0	32	64.0	18	36.0
Venezuela	.	.	8	100.0	8	100.0	.	.
Dom. Repub.	.	.	7	100.0	3	42.9	4	57.1
all countries	236	18.8	1022	81.2	769	61.1	489	38.9

Table 22 : Comparison of number of patients with concomitant medication

		n	%
V1-V3	no	236	18.8
	yes	1022	81.2
V3-V4	no	769	61.1
	yes	489	38.9

Table 23 : Comparison of number of absence days per month

	profession	n	mean	s	min	q1	median	q3	max	missing
V1-V3	occupation	428	0.66	1.54	0.00	0.00	0.00	0.75	12.75	0
	kinderg./school	713	1.72	2.33	0.00	0.00	1.00	2.50	18.00	0
V3-V4	occupation	425	0.34	0.72	0.00	0.00	0.00	0.38	5.00	3
	kinderg./school	713	0.76	1.16	0.00	0.00	0.38	1.25	10.25	0

Table 24 : Efficacy assessment

		n	%
efficacy	missing	4	0.3
	very good	747	59.4
	good	390	31.0
	satisfactory	101	8.0
	insufficient	16	1.3
long-term efficacy	missing	2	0.2
	very good	753	59.9
	good	386	30.7
	satisfactory	93	7.4
	insufficient	24	1.9

Table 25 : Comparison of efficacy assessment

		V4			
V3	missing	very good	good	satisfactory	insufficient
missing	.	3	1	.	.
very good	1	537	173	30	6
good	1	186	165	34	4
satisfactory	.	25	43	26	7
insufficient	.	2	4	3	7

Table 26 : Necessity for further treatment with Luivac/Paspat oral

		n	%
further treatment	missing	7	0.6
	no	640	50.9
	yes	611	48.6