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Study No.: VIAPAED 102318
Title: Steroid-sparing with the salmeterol/fluticasone propionate 50/100µg b.i.d. combination compared to fluticasone propionate 200g b .i.d. alone in the management of children and adolescents with moderate persistent asthma.
Rationale: According to international treatment guidelines for asthma, inhaled corticosteroids (ICS) are the treatment of choice for maintenance therapy in patients with persistent asthma. If patients still have symptoms despite regular low dose ICS, treatment should be increased. Either the inhaled corticosteroid dose can be doubled or additional medication can be added. This study was designed to investigate the steroid-sparing effect of the combination of salmeterol and fluticasone propionate compared to a higher dose of fluticasone propionate alone in the treatment of children and adolescents suffering with moderate persistent asthma.
Phase: IV
Study Period: 03 Nov 2004-12 Apr 2007
Study Design: Prospective, randomised, double-blind, parallel-group multi-centre study comprising a 2-week screening period and an 8-week treatment period. Subjects attended 4 study visits in total. Subjects received an asthma diary for daily recordings of their asthma symptoms, the use of salbutamol as rescue medication and peak flow measurements.
Centres: 57 centres in Germany (39 active centres).
Indication: Moderate persistent asthma.
Treatment: Screening period: fluticasone propionate 2 x 100 g per day; treatment period: salmeterol/fluticasone propionate 50/100 µg b.i.d. or fluticasone propionate 200 µg b.i.d.
Objectives: Non-inferiority with regard to efficacy of twice daily salmeterol/fluticasone propionate (50/100 g) compared to twice daily fluticasone propionate (200 µg).
Primary Outcome/Efficacy Variable: Change in mean morning expiratory peak flow (PEF, L/min) at week 8 of therapy compared to the baseline value (week -1) of the screening period.
Secondary Outcome/Efficacy Variable(s): <ul style="list-style-type: none"> - Asthma symptom score (ASS) on a scale of 0-4 - Number of days (24 h) without asthma symptoms - Use of salbutamol as rescue medication - Number of weeks with successful asthma control - Spirometrically determined FVC, FEV1 and PEF - Mean morning and evening PEF (absolute and in % of predicted normal value for weeks 1-2, 3-4 and 7-8) - Change in mean % predicted morning and evening peak flow - Percentage of subjects with a peak flow variability (morning vs. evening) of > 20% in weeks 4 and 8 - Withdrawals due to asthma exacerbations or adverse events
Statistical Methods: The primary efficacy variable was the peak expiratory flow in the morning, documented daily in the patient's diary. The primary analysis population was the Per Protocol (PP) population. The mean of the last 7 days before randomisation (baseline period) and the mean of the last 7 days of treatment during the study (post-baseline period) were evaluated. The change in the mean peak expiratory flow after 8 weeks of treatment compared to baseline was computed for each patient. Missing values were not replaced. The primary efficacy analysis was a non-inferiority analysis with a non-inferiority margin of $\Delta = 7$ L/min. All tests were performed one-sided with a type I error level of $\alpha = 0.05$. A one-sided t-test was performed for the shifted null hypothesis "combination therapy exhibits an at least by 7 L/min lesser change of average morning peak flow after 8 weeks of treatment minus baseline than fluticasone propionate". For the confirmatory analysis the combined p-value was computed

according to the inverse normal method. If non-inferiority could be statistically confirmed a test for superiority was planned to be performed for the PP population. Superiority was statistically proven if the lower limit of the exact 95% confidence interval for the difference (change of expiratory peak flow under test medication (salmeterol/fluticasone propionate) minus change of expiratory peak flow under control medication (fluticasone propionate) was greater than zero. Both tests (non-inferiority and superiority) were performed at a one-sided significance level of $\alpha=0.05$. This procedure secured an overall significance level of 5% because the test for superiority was only performed in case the non-inferiority of the test medication (salmeterol/fluticasone propionate) could be statistically proven.

The analysis of secondary endpoints was exploratory; summary statistics were provided. The analysis population was the Intent-to-Treat (ITT) population. Adverse events were coded according to MedDRA version 9.1.

Populations were defined as follows: safety population: all randomised subjects who received study medication at least once after randomisation; intention-to-treat population: all subjects included in the safety analysis set for whom at least 1 valid value was documented for the primary efficacy variable at baseline and after baseline; per-protocol population: all subjects included in the intention-to-treat analysis set who did not have any relevant protocol deviations and had at least 47 days of study treatment and non-missing diary recordings.

Please note that the study was prematurely terminated after an adaptive interim analysis (performed due to slow recruitment) had statistically confirmed non-inferiority of salmeterol/fluticasone propionate compared to a higher dose of fluticasone propionate alone.

Study Population: Children and adolescents aged 4-16 years with a history of asthma who had been pre-treated with an inhaled corticosteroid at a dosage of 200-400 μg BDP or equivalent daily during the previous 4 weeks, were to be included into the screening period. Key inclusion criteria for the treatment period were: The presence of asthma symptoms on at least 7 of 14 days of the screening period with a symptom score of at least 2 (sum of day and night); 4 of these 7 days had to be within the last 7 days prior to the randomisation visit. At either visit 1 or visit 2, FEV1 had to have increased at least by 10% compared to baseline, 15 minutes after inhalation of 200 μg salbutamol. Subjects were not to be included into the screening period if (during the last 4 weeks) they had been hospitalised due to bronchial asthma or in case of pneumonia, bronchitis, treatment of respiratory infections with antibiotics, treatment with systemic corticosteroids or treatment with long-acting inhaled beta-2-sympathomimetic agents or with oral beta-2-sympathomimetic agents. Exclusion criteria for the treatment period were the occurrence of an upper respiratory tract infection, bronchitis, pneumonia or asthma exacerbation necessitating treatment with an oral steroid, during the screening period.

	SFC (salmeterol/ fluticasone propionate combination)	FP (fluticasone propionate)
Number of Subjects:		
Planned, N	190	190
Randomised, N	138	145
Completed, n (%)	133 (96.4)	142 (97.9)
Total Number Subjects Withdrawn, N (%)	5 (3.6)	3 (2.1)
Withdrawn due to Adverse Events n (%)	0	0
Withdrawn due to Lack of Efficacy n (%)	Not assessed	Not assessed
Withdrawn for other reasons n (%)	5 (3.6)	3 (2.1)
Demographics	SFC	FP
N (ITT)	137	144
Females: Males	45:92	44:100
Mean age, years (\pm SD)	9.6 \pm 3.1	9.4 \pm 3.1
Race, n (%)	Not recorded	Not recorded

Mean body weight, kg (\pm SD)	39.4 \pm 18.0	39.7 \pm 17.6
Primary Efficacy Results (PP population)		
Mean morning PEF (L/min; mean \pm SD)	SFC (N=84)	FP (N=94)
Baseline period (last 7 days before randomisation)	241.1 \pm 77.1	245.6 \pm 92.2
Post-baseline period (week 8 of therapy)	270.7 \pm 81.0	263.9 \pm 92.7
Change from baseline period	29.6 \pm 29.4	18.3 \pm 34.3
Difference between treatments [95% one-sided CI]	11.3 [3.4; ∞]	
Step 1 testing: non-inferiority (delta = -7 L/min) (p-value, t-test)	< 0.0001	
Step 2 testing: superiority (p-value, t-test)	0.0098	
Secondary Outcome Variable(s): ITT population		
Mean asthma symptom score (scale 0-4) - night (mean \pm SD)	SFC (N=137)	FP (N=144)
Baseline period (last 7 days before randomisation)	0.9 \pm 0.7	0.9 \pm 0.6
Post-baseline period (week 8 of therapy)	0.4 \pm 0.7	0.4 \pm 0.5
Change from baseline period	-0.5 \pm 0.6	-0.5 \pm 0.6
Difference between LSMEANS for change from baseline period	0.01	
95% CI	[-0.11; 0.13]	
Mean asthma symptom score (scale 0-4) - day (mean \pm SD)	SFC	FP
Baseline period (last 7 days before randomisation)	1.2 \pm 0.7	1.3 \pm 0.7
Post-baseline period (week 8 of therapy)	0.5 \pm 0.7	0.5 \pm 0.7
Change from baseline period	-0.8 \pm 0.8	-0.8 \pm 0.8
Difference between LSMEANS for change from baseline period	0.02	
95% CI	[-0.14; 0.18]	
Percentage of days without asthma symptoms (mean \pm SD)	SFC	FP
Screening period	20.9 \pm 24.3	19.3 \pm 25.6
Randomised treatment period	62.4 \pm 35.3	52.9 \pm 36.5
Change from screening period	41.5 \pm 34.5	33.3 \pm 31.4
Difference between LSMEANS for change from screening period	8.7	
95% CI	[1.2; 16.3]	
Mean daily number of additional salbutamol administrations (mean \pm SD)	SFC	FP
Baseline period (last 7 days before randomisation)	1.7 \pm 1.2	1.6 \pm 1.0
Post-baseline period (week 8 of therapy)	0.6 \pm 1.2	0.6 \pm 1.0
Change from baseline period	-1.1 \pm 1.3	-1.0 \pm 1.0
Difference between LSMEANS for change from baseline period	-0.03	
95% CI	[-0.27; 0.20]	
Percentage of days without use of salbutamol (mean \pm SD)	SFC	FP
Screening period	20.3 \pm 23.8	18.6 \pm 24.8
Randomised treatment period	60.2 \pm 34.4	51.4 \pm 35.6
Change from screening period	39.9 \pm 33.3	32.4 \pm 30.7
Difference between LSMEANS for change from screening period	8.0	

95% CI	[0.6; 15.3]	
Number of weeks with successful asthma control (mean \pm SD)	3.4 \pm 2.7	2.7 \pm 2.7
Spirometry: PEF (% of predicted normal value) (mean \pm SD)	SFC	FP
Visit 2 (randomisation)	86.6 \pm 22.8	86.6 \pm 19.0
Visit 4 (after 8 weeks of treatment)	100.2 \pm 25.0	95.4 \pm 21.1
Change from visit 2	13.8 \pm 21.8	8.6 \pm 17.5
Difference between LSMEANS for change from visit 2	6.1	
95% CI	[1.8; 10.4]	
Spirometry: FEV1 (% of predicted normal value) (mean \pm SD)	SFC	FP
Visit 2 (randomisation)	91.1 \pm 19.7	92.1 \pm 14.6
Visit 4 (after 8 weeks of treatment)	101.0 \pm 15.6	100.8 \pm 16.9
Change from visit 2	9.7 \pm 16.2	7.9 \pm 13.8
Difference between LSMEANS for change from visit 2	1.9	
95% CI	[-1.2; 5.0]	
Spirometry: FVC (% of predicted normal value) (mean \pm SD)	SFC	FP
Visit 2 (randomisation)	86.8 \pm 19.2	87.8 \pm 13.3
Visit 4 (after 8 weeks of treatment)	94.2 \pm 14.9	96.2 \pm 15.8
Change from visit 2	7.4 \pm 15.1	8.0 \pm 12.0
Difference between LSMEANS for change from visit 2	-0.5	
95% CI	[-3.2; 2.3]	
Mean morning PEF (L/min; mean \pm SD)	SFC	FP
Weeks (-2)-(-1) (screening period)	242.5 \pm 82.8	243.5 \pm 87.2
Weeks 1-2	264.2 \pm 87.6	251.6 \pm 90.0
Weeks 3-4	267.7 \pm 87.5	256.4 \pm 88.1
Weeks 5-6	269.7 \pm 91.4	258.8 \pm 90.8
Weeks 7-8	269.8 \pm 90.3	260.0 \pm 88.8
Mean morning PEF (% of predicted normal value; mean \pm SD)	SFC	FP
Weeks (-2)-(-1) (screening period)	85.8 \pm 16.9	85.4 \pm 15.4
Weeks 1-2	93.6 \pm 17.3	88.5 \pm 15.6
Weeks 3-4	95.1 \pm 17.8	90.5 \pm 15.4
Weeks 5-6	95.1 \pm 19.0	91.2 \pm 16.0
Weeks 7-8	95.0 \pm 19.4	91.6 \pm 16.2
Mean evening PEF (L/min; mean \pm SD)	SFC	FP
Weeks (-2)-(-1) (screening period)	248.6 \pm 83.0	249.0 \pm 87.8
Weeks 1-2	269.2 \pm 87.9	255.6 \pm 88.5
Weeks 3-4	272.9 \pm 88.3	259.7 \pm 87.8
Weeks 5-6	274.6 \pm 89.9	260.9 \pm 90.2
Weeks 7-8	274.4 \pm 90.2	262.7 \pm 89.5
Mean evening PEF (% of predicted normal value; mean \pm SD)	SFC	FP
Weeks (-2)-(-1) (screening period)	88.1 \pm 17.0	87.5 \pm 15.4
Weeks 1-2	95.6 \pm 18.1	90.1 \pm 15.1
Weeks 3-4	97.2 \pm 18.7	91.8 \pm 15.4
Weeks 5-6	97.1 \pm 19.0	92.2 \pm 16.2

Weeks 7-8	96.9 ± 19.8	92.4 ± 16.6
Mean morning PEF (% of predicted normal value; mean ± SD)	SFC	FP
Baseline period (last 7 days before randomisation)	86.2 ± 17.1	86.2 ± 16.5
Post-baseline period (week 8 of therapy)	95.6 ± 19.9	92.4 ± 16.2
Change from baseline period	9.2 ± 13.8	6.3 ± 11.9
Difference between LSMEANS for change from baseline period	3.0	
90% CI	[0.5; 5.5]	
Mean evening PEF (% of predicted normal value; mean ± SD)	SFC	FP
Baseline period (last 7 days before randomisation)	88.2 ± 17.7	87.9 ± 16.4
Post-baseline period (week 8 of therapy)	97.7 ± 20.5	93.2 ± 16.8
Change from baseline period	9.4 ± 13.2	5.4 ± 12.7
Difference between LSMEANS for change from baseline period	4.1	
95% CI	[1.1; 7.1]	
Percentage of subjects with a peak flow variability >20%	SFC	FP
Mean peak flow variability >20% during week 4 (% of subjects)	3.7	2.1
Mean peak flow variability >20% during week 8 (% of subjects)	2.2	4.2
Percentage of withdrawals due to asthma exacerbation, intolerance or rejection of the study medication	0	0
Safety Results: Analysis of AEs was differentiated by timing of occurrence: before randomisation (screening period) or at or after randomisation (randomised treatment period = treatment emergent). In the following, treatment emergent AEs are presented.		
	SFC (N=137)	FP (N=145)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s)	43 (31.4)	44 (30.3)
Nasopharyngitis	5 (3.7)	8 (5.5)
Pyrexia	4 (2.9)	6 (4.1)
Bronchitis	4 (2.9)	3 (2.1)
Respiratory tract infection	4 (2.9)	3 (2.1)
Viral infection	4 (2.9)	0 (0.0)
Upper respiratory tract infection	3 (2.2)	1 (0.7)
Headache	2 (1.5)	4 (2.8)
Rhinitis	2 (1.5)	4 (2.8)
Acute tonsillitis	2 (1.5)	3 (2.1)
Conjunctivitis	2 (1.5)	2 (1.4)
Sinusitis	2 (1.5)	2 (1.4)
Viral upper respiratory tract infection	2 (1.5)	1 (0.7)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
Subjects with non-fatal SAEs, n (%) [related]		
Tachycardia	1 (0.7) [1]	0
Meningitis	1 (0.7) [0]	0
Sinus operation	0	1 [0]
Subjects with fatal SAEs, n (%) [related]	0	0

Conclusion:

The mean change from baseline in morning PEF was significantly greater with salmeterol and fluticasone propionate (50/100 g) b .i.d. compared to fluticasone propionate (200 µg) b.i.d alone. Changes in mean evening PEF, the number of days without asthma symptoms / additional usage of salbutamol and the number of weeks with successful asthma control also favoured the combination treatment over higher dose fluticasone propionate alone. Frequency and nature of adverse events reported in this study were similar in both treatment groups.

Publications: No Publication

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