Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Sifrol®, Mirapexin®		**EudraCT No.:** 2006-006431-42	
Name of active ingredient: Pramipexole		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 21 JAN 2009	**Trial No. / U No.:** 248.629 / U09-1047-01	**Dates of trial:** 8 MAY 2007 – 3 JUL 2008	**Date of revision:** Not applicable

Title of trial:	A phase IV randomised, double-blind, placebo-controlled, dose titration trial with pramipexole (Sifrol®, Mirapexin®) 0.125-0.75 mg/day per os to investigate the long-term efficacy, safety and tolerability in patients with idiopathic moderate to severe Restless Legs Syndrome for 26 weeks
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, conducted at 42 sites in 9 countries across Europe
Publication (reference):	Data from this study have not been published.
Clinical phase:	IV
Objectives:	The objective of the study was the evaluation of the long-term efficacy of 26 weeks of treatment with pramipexole in patients with idiopathic moderate to severe Restless Legs Syndrome (RLS) in comparison with placebo. In addition, the effects of pramipexole on augmentation, rebound (worsening of RLS symptoms following treatment discontinuation), quality of life and safety were considered.
Methodology:	This was a randomised, placebo-controlled, double-blind, parallel-group, flexible dose-titration (based on efficacy and tolerability) trial, conducted over 26 weeks.
No. of subjects:	
planned:	entered: 320
actual:	enrolled: 497
	entered: 331
	Pramipexole: entered: 168 treated: 166 analysed for primary endpoint: 162 Placebo: entered: 163 treated: 163 analysed for primary endpoint: 159

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Diagnosis and main criteria for inclusion:	The study population comprised male or female patients aged 18 to 85 years with a diagnosis of idiopathic RLS, according to the clinical criteria of the International Restless Legs Syndrome Study Group, with a International Restless Legs Syndrome Study Group Rating Scale (IRLS) total score of >15 at baseline, who had experienced symptoms for at least 2 to 3 days per week during the 3 months prior to baseline.
Test product:	Pramipexole tablets (0.25 mg)
dose:	4 weeks of flexible dose-titration (to optimise efficacy and tolerability), starting at 0.125 mg once daily with the potential to increase or decrease the dose in steps to 0.25 mg, 0.5 mg and 0.75 mg, with the final dose level subsequently fixed for 22 weeks.
mode of admin.:	Oral, once daily in the evening (2 to 3 hours before bedtime)
batch no.:	B071000206 (Lot 608360)
Reference therapy:	Matching placebo tablets
dose:	4 weeks of flexible dose-titration as for the investigational product; with the dose subsequently fixed for 22 weeks.
mode of admin.:	Oral, once daily in the evening (2 to 3 hours before bedtime)
batch no.:	B061002596 (Lot 606960U)
Duration of treatment:	26 weeks, with a 4-week dose-titration phase and a 22-week fixed-dose phase.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint assessed the change from baseline after 26 weeks of treatment in IRLS total score following treatment with pramipexole, in comparison with placebo. Secondary efficacy endpoints considered: Clinical Global Impressions - Global Improvement (CGI-I) responder rate; IRLS responder rate; Patient Global Impression (PGI) responder rate; and change from baseline in RLS-6 score, mood disturbance (item 10 of the IRLS scale), Visual Analogue Scale (VAS) score for pain in limbs, RLS quality of life score (RLS-QoL), and Short Form 36 (SF-36) quality of life instrument dimensions.

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	The response criteria used to formally identify a difference between pramipexole and placebo treatment comprised: change in IRLS total score from baseline, CGI-I responder rate (of at least "much improved") and IRLS responder rate (at least 50% reduction from baseline in IRLS total score).
Safety:	Safety was assessed in terms of: adverse event (AE) profile, incidence and severity of augmentation (based on international diagnostic criteria and blinded expert panel rating), the incidence of worsening severity of RLS symptoms following treatment discontinuation, change from baseline in systolic and diastolic blood pressure (supine and standing) and change from baseline in pulse rate (supine and standing).
Statistical methods:	The primary objective of the trial, assessing the long-term efficacy of pramipexole on RLS symptoms compared with placebo, was considered using a system of hierarchically-ordered, 2-sided statistical tests. The primary efficacy analysis considered the mean change in IRLS total score from baseline, and was assessed using a baseline-adjusted Analysis of Covariance model. The study design stipulated a closed testing procedure whereby, if the primary analysis established superiority for pramipexole treatment, the CGI-I responder rate and then IRLS responder rate were to be sequentially tested using the Cochran-Mantel-Haenszel test. The secondary endpoint PGI responder rate was tested using the Cochran-Mantel-Haenszel test. RLS-6 scores, the IRLS item 10 score, VAS score for pain in limbs, RLS-QoL total score and SF-36 dimensions underwent exploratory analysis, with pooled country stratification using the van Elteren test.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	Most patients entered into the study were white (100.0% in the pramipexole group and 99.4% in the placebo group) and female (61.4% vs. 57.7%); the mean age of patients in the pramipexole group was slightly higher (57.9 years) than in the placebo group (55.8 years). At baseline the mean IRLS total score was 23.9 for patients in the pramipexole group and 23.5 for those in the placebo group. The treatment groups were well matched for baseline characteristics.

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Efficacy / clinical Pharmacology results continued:

A total of 329 patients were treated in either the pramipexole (166 patients) or placebo (163 patients) groups. Of these, 95 patients discontinued study participation prematurely, comprising 21.1% in the pramipexole treatment group and 36.8% in the placebo group; 11.4% of patients in the pramipexole group and 14.1% of patients in the placebo group withdrew due to AEs; 2.4% of patients in the pramipexole and 15.3% in the placebo group withdrew due to lack of efficacy.

In the primary analysis population (Full Analysis Set with the last observation carried forward) of 321 patients, 26 weeks of double-blind treatment led to an adjusted mean change in IRLS total score from baseline of -13.7 (standard error [SE] = 0.8) for pramipexole, while placebo treatment resulted in an adjusted mean change of -11.1 (SE = 0.8). The corresponding adjusted mean treatment difference of -2.6 (SE = 1.0) was statistically significant (p = 0.0077) in favour of pramipexole.

A total of 68.5% of patients in the pramipexole group were considered CGI-I responders compared with 50.3% in the placebo group, representing a statistically significant treatment difference (p = 0.001) in favour of pramipexole. A statistically significant treatment benefit for pramipexole was also seen in terms of IRLS responder rate (≥50% reduction in total score), with response achieved for 58.6% of patients in the active treatment group and 42.8% of patients in the placebo group (p = 0.0044).

A statistically significant treatment benefit for pramipexole was also apparent in terms of RLS-6 night-time symptoms 'Satisfaction with sleep during the last 7 nights' (p = 0.0489) and 'Severity of RLS symptoms at falling asleep' (p = 0.0315), after 26 weeks of treatment. RLS-6 daytime symptoms did not show a treatment difference between pramipexole and placebo. No difference in IRLS item 10 score (mood disturbance) was associated with pramipexole treatment. A median reduction in VAS score for pain in limbs of -26.0 was seen for the pramipexole group and of -15.0 for the placebo group after 26 weeks of treatment but the difference did not achieve statistical significance.

An improvement in RLS-Quality of Life was not demonstrated for pramipexole over that seen for placebo. Of the SF-36 dimensions, bodily pain (median difference 2.0; 95% confidence interval [CI] 1.6, 2.4) and vitality (median difference 6.3; 95% CI 5.9, 6.6) showed a statistically significant treatment benefit for pramipexole.

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Safety results:

A total of 329 patients entered the trial and received at least one dose of study medication. Patients were treated with tablets containing 0.25 mg pramipexole or matching placebo, and achieved a mean final dose of 1.7 tablets/day (0.4 mg/day) in the pramipexole group and 2.0 tablets/day in the placebo group. The median duration of study drug exposure was 182 days for both treatment groups. The pramipexole dose being taken by patients at the end of the study was 0.125 mg for 27 patients (16.3%), 0.25 mg for 53 patients (31.9%), 0.5 mg for 44 patients (26.5%) and 0.75 mg for 42 patients (25.3%). The matching placebo dose being taken by patients at the end of the study was 0.125 mg for 17 patients (10.4%), 0.25 mg for 29 patients (17.8%), 0.5 mg for 57 patients (35.0%) and 0.75 mg for 60 patients (36.8%).

A total of 120 patients (72.3%) in the pramipexole group and 106 patients (65.0%) in the placebo group experienced AEs, with the frequency of AEs being comparable for the pramipexole final dose groups. The most frequent AEs by system organ class were nervous system disorders (27.7% in the pramipexole group vs. 27.0% in the placebo group), infections and infestations (18.1% vs. 26.4%), musculoskeletal and connective tissue disorders (24.7% vs. 16.0%), gastrointestinal disorders (25.9% vs. 14.1%), general disorders and administration site conditions (16.3% vs. 14.1%), and psychiatric disorders (16.3% vs. 12.9%). The most frequent AEs in the pramipexole treatment group were nausea (14.5% vs. 3.7% in the placebo group) and fatigue (10.8% vs. 9.2%). There was no indication that a higher final treatment dose was associated with an increased incidence of specific AEs.

The incidence of severe AEs was comparable for the treatment groups (10.2% for the pramipexole vs. 9.2% for the placebo groups). The most common severe AEs were extremity pain (2.4% vs. 0%) and RLS (1.8% vs. 1.2%).

AEs considered drug-related, in the opinion of the investigator, occurred in 38.6% of patients in the pramipexole group and 30.7% of patients in the placebo group. The most frequently reported drug-related AEs in the pramipexole group were nausea (10.2% vs. 1.8%), fatigue (9.0% vs. 6.1%) and somnolence (6.6% vs. 4.3%). The incidence of drug-related AEs was comparable across the final pramipexole dose groups (44.4% at 0.125 mg, 18.9% at 0.25 mg, 29.5% at 0.5 mg, and 23.8% at 0.75 mg).

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Safety results continued:

AEs leading to early discontinuation of the trial drug were seen in 11.4% of patients in the pramipexole group and 14.1% of patients in the placebo group. The most common AEs leading to treatment discontinuation included: nausea (3.0% vs. 1.2%), RLS (0.6% in the pramipexole group vs. 3.1% in the placebo group) and fatigue (1.8% vs. 1.2%).

No deaths occurred during the trial. In total, 8 patients (4.8%) in the pramipexole group and 3 patients (1.8%) in the placebo group experienced serious AEs. SAEs experienced by patients in the pramipexole treatment group comprised: neck pain with extradural haematoma, haemorrhoidal haemorrhage, chronic obstructive pulmonary disease, myocardial infarction, urinary tract infection, uterine prolapse, intervertebral disc protrusion and humerus fracture. All apart from the urinary tract infection resolved. No SAEs occurring in the pramipexole group were considered treatment-related but events of orthostatic hypotension and vomiting in a patient in the placebo group were.

Other significant AEs (non-serious AEs leading to dose reduction or discontinuation) were recorded for 16.3% of patients in the pramipexole group and 16.0% in the placebo group. The most common other significant AEs included nausea (4.2% vs. 1.2%), RLS (0.6% in the pramipexole group vs. 3.7% in the placebo group) and fatigue (2.4% vs. 1.8%).

Eighteen patients (11.8%) in the pramipexole group and 14 patients (9.4%) in the placebo group experienced events classified, by a blinded expert panel, as augmentation. Kaplan-Meier analysis of time to augmentation showed that there was no significant difference in the risk of augmentation developing between treatment groups ($p = 0.8060$). Analysis resulted in augmentation survival estimates at Visit 10 of 0.8560 for the pramipexole group and 0.8855 for the placebo group. Of patients experiencing augmentation, most continued taking the study treatment for ≥168 days (15 patients [83.3%] in the pramipexole group and 8 patients [57.1%] in the placebo group). Of patients with classified augmentation, 3 of 18 who received pramipexole discontinued the study at the time of augmentation compared with 5 of 14 patients receiving placebo. A worsening of IRLS total score from baseline was seen in 5 of 18 patients in the pramipexole group with classified augmentation and 3 of 14 patients in the placebo group.

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Safety results continued:

The potential for RLS symptoms to worsen beyond baseline (by at least 4 points in IRLS total score) following abrupt discontinuation of pramipexole treatment was demonstrated in 10.4% of patients; of placebo treated patients 1.5% experienced worsening symptoms. There was no evidence of a relationship between the final pramipexole dose and the worsening of RLS.

Analysis of vital sign parameters did not show any clinically relevant changes. The incidence of orthostatic reactions in the two treatment groups was low. In the pramipexole group no patient experienced an orthostatic reaction at screening or baseline, 1 patient (0.6%) each experienced an orthostatic reaction at Weeks 4, 12 and 26, and 3 patients (1.8%) experienced an orthostatic reaction at follow up. In the placebo group 2 patients (1.2%) experienced an orthostatic reaction at screening, 1 patient (0.6%) each experienced an orthostatic reaction at Weeks 4 and 12, and 2 patients (1.2%) experienced an orthostatic reaction at Week 26.

Conclusions:

In this population of patients with idiopathic RLS who received treatment over 26 weeks, pramipexole demonstrated sustained efficacy and a treatment benefit as compared with placebo in terms of IRLS, CGI and PGI. A pramipexole treatment benefit was also demonstrated for SF-36 quality of life parameters of bodily pain and vitality. Pramipexole treatment was safe and well tolerated. Kaplan-Meier analysis of time to augmentation showed that there was no significant difference in the risk of augmentation, as defined by current criteria, between pramipexole and placebo. Following abrupt discontinuation of pramipexole therapy, about 10% of patients experienced a worsening of RLS symptoms from their baseline status.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement secondary endpoints of the trial.

Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Patient Global Impression (PGI) Responder Rate after 26 weeks	Table 15.2.2.3: 1
Change from baseline in RLS-6 Score "Severity During the Day When at Rest" after 26 weeks	Table 15.2.2.4: 7
Change from baseline RLS-6 Score "Severity During the Day Engaged in Activities" after 26 weeks	Table 15.2.2.4: 9
Change from baseline in RLS-6 Score "Tired or Sleepy During the Day" after 26 weeks	Table 15.2.2.4: 11
Change from baseline in IRLS Mood Disturbance Score (Item 10) after 26 weeks	Table 15.2.2.5: 1
Change from baseline in Visual Analogue Scale (VAS) Score for Pain in Limbs after 26 weeks	Table 15.2.2.6: 1
Change from baseline in Quality of Life in RLS (RLS QoL) Score after 26 weeks	Table 15.2.2.7: 1
Change from baseline in Short Form-36 (SF-36) Dimension Bodily Pain after 26 weeks	Table 15.2.2.8: 1
Change From Baseline in SF-36 Dimension Vitality After 26 Weeks	Table 15.2.2.8: 15
Change From Baseline in SF-36 Dimension General Health After 26 Weeks	Table 15.2.2.8: 3

Table 15.2.2.3: 1 Analysis of Patient Global Impression responder rate / FAS, LOCF
CMH test with pooled country stratification
at visit 10 (after 26 weeks)

		PGI Response					
		Placebo		Pramipexole		Total	
Pooled country	Response	N	%	N	%	N	%
-All-	All	159	100.0	162	100.0	321	100.0
	Non-responder	89	56.0	61	37.7	150	46.7
	Responder	70	44.0	101	62.3	171	53.3
Austria+Slowakia	All	7	100.0	8	100.0	15	100.0
	Non-responder	5	71.4	2	25.0	7	46.7
	Responder	2	28.6	6	75.0	8	53.3
Belgium+Spain	All	10	100.0	10	100.0	20	100.0
	Non-responder	4	40.0	3	30.0	7	35.0
	Responder	6	60.0	7	70.0	13	65.0
Finland	All	26	100.0	26	100.0	52	100.0
	Non-responder	18	69.2	9	34.6	27	51.9
	Responder	8	30.8	17	65.4	25	48.1
Germany	All	41	100.0	42	100.0	83	100.0
	Non-responder	28	68.3	14	33.3	42	50.6
	Responder	13	31.7	28	66.7	41	49.4
Ireland	All	13	100.0	11	100.0	24	100.0
	Non-responder	6	46.2	5	45.5	11	45.8
	Responder	7	53.8	6	54.5	13	54.2
Netherlands	All	21	100.0	23	100.0	44	100.0
	Non-responder	8	38.1	8	34.8	16	36.4
	Responder	13	61.9	15	65.2	28	63.6
United Kingdom	All	41	100.0	42	100.0	83	100.0
	Non-responder	20	48.8	20	47.6	40	48.2
	Responder	21	51.2	22	52.4	43	51.8
p-value	CMH	vs.	Placebo		0.0011		

Table 15.2.2.4: 7 Analysis of RLS-6 'Severity of RLS symptoms during the day when at rest' after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

RLS-6 'daytime severity at rest'	Placebo	Pramipexole
Number of patients	159	162
Baseline		
Median [P25%,P75%]	4.0 [2.0,6.0]	4.0 [2.0,6.0]
Treatment phase		
Median [P25%,P75%]	1.0 [0.0,4.0]	1.0 [0.0,3.0]
Change from baseline		
Median [P25%,P75%]	-1.0 [-4.0,0.0]	-1.0 [-4.0,0.0]
Difference from Placebo°		
Median		0.0
95% CI for median		[-0.0, 0.0]
p-value°		0.8410

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.4: 9 Analysis of RLS-6 'Severity of RLS symptoms during the day when not at rest but engaged in activities' after 26 weeks / FAS, LOCF at visit 10 (after 26 weeks)

RLS-6 'daytime severity engaged in activities'	Placebo	Pramipexole
Number of patients	159	162
Baseline		
Median [P25%,P75%]	1.0 [0.0,2.0]	1.0 [0.0,2.0]
Treatment phase		
Median [P25%,P75%]	0.0 [0.0,1.0]	0.0 [0.0,1.0]
Change from baseline		
Median [P25%,P75%]	0.0 [-1.0,0.0]	0.0 [-1.0,0.0]
Difference from Placebo°		
Median		0.0
95% CI for median		[-0.0, 0.0]
p-value°		0.9241

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.4: 11 Analysis of RLS-6 'Tired or sleepy during the day' after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

RLS-6 'tiredness at day'	Placebo	Pramipexole
Number of patients	159	162
Baseline Median [P25%,P75%]	4.0 [2.0,6.0]	4.0 [2.0,6.0]
Treatment phase Median [P25%,P75%]	2.0 [1.0,5.0]	1.0 [0.0,4.0]
Change from baseline Median [P25%,P75%]	-1.0 [-3.0,0.0]	-1.0 [-3.0,0.0]
Difference from Placebo° Median		0.0
95% CI for median		[-0.0, 0.0]
p-value°		0.8093

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.5: 1 Analysis of IRLS item 10 score after 26 weeks / FAS, LOCF

at visit 10 (after 28 weeks)

IRLS item 10 score	Placebo	Pramipexole
Number of patients	159	162
Baseline		
Median [P25%,P75%]	2.0 [1.0,2.0]	2.0 [1.0,3.0]
Treatment phase		
Median [P25%,P75%]	0.0 [0.0,1.0]	0.0 [0.0,1.0]
Change from baseline		
Median [P25%,P75%]	-1.0 [-2.0,0.0]	-1.0 [-2.0,0.0]
Difference from Placebo°		
Median		0.0
95% CI for median		[-0.0, 0.0]
p-value°		0.0583

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.6: 1 Analysis of VAS score for pain in limbs after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

VAS score for pain in limbs	Placebo	Pramipexole
Number of patients	158	162
Baseline		
Median [P25%,P75%]	55.0 [36.0,73.0]	50.0 [33.0,68.0]
Treatment phase		
Median [P25%,P75%]	27.0 [2.0,59.0]	16.0 [3.0,37.0]
Change from baseline		
Median [P25%,P75%]	-15.0 [-46.0,0.0]	-26.0 [-47.0,-5.0]
Difference from Placebo°		
Median		-5.0
95% CI for median		[-5.5, -4.5]
p-value°		0.0916

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.7: 1 Analysis of Quality of Life (RLS-QoL) after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

RLS-Quality of Life	Placebo	Pramipexole
Number of patients	153	157
Baseline		
Median [P25%,P75%]	70.0 [57.5,82.5]	72.5 [60.0,82.5]
Treatment phase		
Median [P25%,P75%]	87.5 [72.5,97.5]	90.0 [77.5,97.5]
Change from baseline		
Median [P25%,P75%]	12.5 [2.5,27.5]	15.0 [5.0,25.0]
Difference from Placebo°		
Median		2.5
95% CI for median		[2.2, 2.8]
p-value°		0.5905

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.8: 1 Analysis of SF36 bodily pain after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

SF-36 bodily pain	Placebo	Pramipexole
Number of patients	152	157
Baseline Median [P25%,P75%]	52.0 [41.0,74.0]	52.0 [41.0,72.0]
Treatment phase Median [P25%,P75%]	62.0 [51.0,84.0]	72.0 [51.0,84.0]
Change from baseline Median [P25%,P75%]	9.0 [-1.0,24.5]	12.0 [0.0,31.0]
Difference from Placebo° Median		2.0
95% CI for median		[1.6, 2.4]
p-value°		0.0179

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.8: 15 Analysis of SF36 vitality after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

SF-36 vitality	Placebo	Pramipexole
Number of patients	152	155
Baseline Median [P25%,P75%]	56.3 [43.8,68.8]	56.3 [37.5,68.8]
Treatment phase Median [P25%,P75%]	56.3 [43.8,75.0]	62.5 [50.0,75.0]
Change from baseline Median [P25%,P75%]	3.1 [-6.3,12.5]	6.3 [0.0,18.8]
Difference from Placebo° Median		6.3
95% CI for median		[5.9, 6.6]
p-value°		0.0206

°Van Elteren test stratified for pooled country for change from baseline

Table 15.2.2.8: 3 Analysis of SF36 general health after 26 weeks / FAS, LOCF

at visit 10 (after 26 weeks)

SF-36 general health	Placebo	Pramipexole
Number of patients	152	155
Baseline Median [P25%,P75%]	67.0 [50.0,82.0]	67.0 [50.0,82.0]
Treatment phase Median [P25%,P75%]	67.0 [52.0,82.0]	67.0 [57.0,82.0]
Change from baseline Median [P25%,P75%]	0.0 [-5.0,10.0]	0.0 [-5.0,10.0]
Difference from Placebo° Median		2.0
95% CI for median		[1.7, 2.3]
p-value°		0.5450

°Van Elteren test stratified for pooled country for change from baseline