STUDY SYNOPSIS

Name of sponsor: Fresenius Kabi Deutschland GmbH	**Individual study table:** Referring to Part of the Dossier Volume: Page:	**(For National Authority Use Only)**
Name of finished product: Neodolpasse® solution for i.v. infusion		
Name of active ingredient: Diclofenac, Orphenadrine		

Title of study:	Efficacy of Neodolpasse® Infusion Solution in the treatment of postoperative pain: Morphine sparing effect during the first 24 hours postoperatively after primary cementless unilateral total hip arthroplasty. A double-blind, placebo-controlled, multi-centre study.
Coordinating Investigator (Principal Investigator in Centre No. 1):	Univ.-Prof. Dr. Hans Gombotz AKH Linz Krankenhausstrasse 9 A-4021 Linz, Austria
Principal Investigator in Centre No. 2:	Prim. Dr. Rudolf Sigl BHS Linz St. Vincent's Hospital Seilerstätte 4 A-4010 Linz, Austria
Principal Investigator in Centre No. 3	Prim. Dr. Helmut Trimmel AOKH Wiener Neustadt Corvinusring 3-5 A-2700 Wiener Neustadt, Austria
Trial Monitor:	Dr. Andrea Gschanes CIS-Services Eggenreich & Gschanes OEG Grazbachgasse 5/7/49 8010 Graz, Austria
Study centres:	Department of Anaesthesiology and Intensive Care Medicine General Hospital (AKH) Linz, Krankenhausstrasse 9, A-4021 Linz, Austria Department of Anaesthesiology and Intensive Care Medicine St. Vincent's Hospital (BHS Linz), Seilerstätte 4, A-4010 Linz, Austria Department for Anaesthesiology and Intensive Care Medicine General Hospital (AOKH) Wiener Neustadt, Corvinusring 3-5, A-2700 Wiener Neustadt, Austria
Publication (reference):	None

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Study period:	First patient included: 27 Apr 2005, last patient completed: 30 Jun 2006. **Phase of development:** III
Objectives:	Primary objective: To evaluate the efficacy of Neodolpasse® Infusion Solution measured by a reduction of the demand for additional analgesic medication via patient controlled analgesia (PCA). Secondary objectives: To evaluate the subjective pain relief over the first 24 hours after the surgical intervention by using a Visual Analogue Scale (VAS) and a Verbal Rating Scale (VRS) system. To evaluate the antipyretic efficacy and the local and systemic tolerability and safety of the Neodolpasse® Infusion Solution.
Methodology:	Double-blind, randomised, placebo controlled, parallel-group, multi-centre trial.

Number of patients:

	All patients	Neodolpasse	Placebo
Screened	127		
Enrolled, randomised and treated	120	60	60
Full analysis set	120	60	60
Per-protocol set	112	59	53

Diagnosis and main criteria for inclusion:	Age:	between 18 and 85 years
	Sex:	both sexes
	Indication:	Postoperative analgesia after primary cementless unilateral total hip arthroplasty under spinal anaesthesia
Test product, dose and mode of administration, batch number:	250 ml Neodolpasse® solution for i.v. infusion containing 75 mg diclofenac and 30 mg orphenadrine-citrate. Two (2) infusions lasting 60 - 90 minutes each were to be administered at a time interval of 12 hours. Batch No.: E100015 (expiry date: 04/2006), F120029 (expiry date: 06/2007)	
Duration of treatment:	The patients received 2 infusions of study medication each lasting 60 - 90 minutes within the first 24 hours post-surgery. The follow-up period was 3 - 10 days post-surgery.	

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Reference therapy, dose and mode of administration, batch number:	250 ml isotonic saline solution (NaCl) for i.v. infusion. Two (2) infusions lasting 60 - 90 minutes each were to be administered at a time interval of 12 hours. Batch No.: E021508 (expiry date: 02/2009), F051501 (expiry date: 06/2010)
Criteria for evaluation	
Safety:	The local and systemic tolerance and safety of Neodolpasse® was to be assessed in comparison to placebo by the laboratory safety values, vital signs and by the adverse event profile until the end of the follow-up period.
Efficacy:	Primary variable: Total morphine dose delivered by PCA pump during the first 24 hours post-surgery Secondary variables: VAS and VRS pain score, incidence of pyrexia, systemic drug safety
Statistical methods:	This was a confirmatory study. Superiority of Neodolpasse® treatment was to be concluded if the total dose of morphine delivered by PCA pump during the first 24 hours post-surgery was lower in the Neodolpasse group than in the placebo group. For confirmatory hypothesis testing at the interim analyses as well as at the final analysis, the inverse normal method of combining the p-values of the two-sample t-test was employed. For estimating the treatment effect, the difference in the total dose of morphine delivered by PCA pump during the first 24 hours post-surgery between treatment groups and the corresponding 95% two-sided repeated confidence interval (RCI) were provided. All other group comparisons were hypothesis generating in nature, i.e., p-values resulting from these statistical tests were interpreted in the exploratory sense. Furthermore, data from all assessments were tabulated and/or plotted using descriptive statistical methods. Standard summary statistics and two-sided 95% confidence intervals were calculated as appropriate. Nominal data were presented in frequency tables. Individual patient data listings were prepared by variable. Missing data were not replaced unless absolutely indicated.

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Summary - conclusions:

Efficacy:

Primary efficacy variable

The total dose of PCA morphine required over the first 24 hours post-surgery was lower in the Neodolpasse than in the placebo group at the first and second interim analysis as well as at the final analysis.

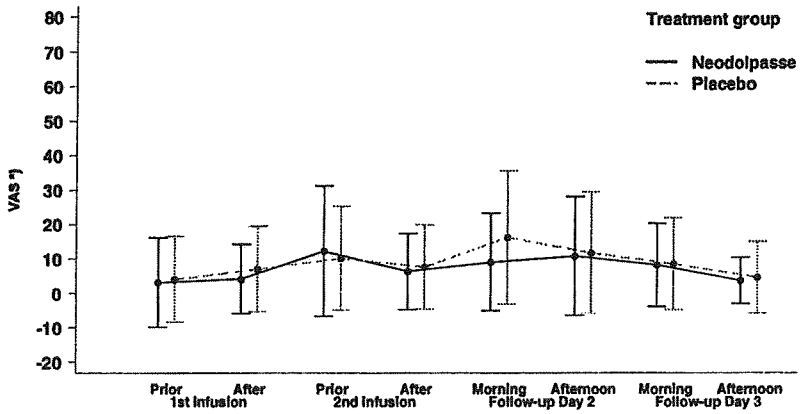
	Data set	Neodolpasse Mean (SD) n	Placebo Mean (SD) n	Observed p-value / α* test stat. / crit. value**
1st interim	FAS	35.5 (16.3) 18	61.7 (33.9) 21	0.0025 / 0.0003*
2nd interim	FAS	37.0 (23.0) 41	58.1 (29.5) 40	3.344 / 2.454**
Final analysis	FAS	38.67 (21.33) 60	55.89 (31.10) 60	3.326 / 2.004**
	PP	38.93 (21.41) 59	59.91 (29.89) 53	4.007 / 2.004**

Differences in the total dose of PCA morphine between treatment groups were statistically significant from the second interim analysis.

Secondary efficacy variables

The total dose of PCA morphine required during the total time of PCA installation was lower in the Neodolpasse (45.01 ± 26.74 [42.50] mg) than in the placebo group (64.25 ± 41.38 [56.00] mg) in a statistically significant way.

Subjective pain intensity assessed by the VAS was generally low from post-surgery to the afternoon of follow-up Day 3. The course of subjective pain intensity over time was almost congruent in both groups.



*) Visual analogue scale (VAS): 0 mm = no pain; 100 mm = maximum imaginable pain intensity.

Means and standard deviations are displayed.

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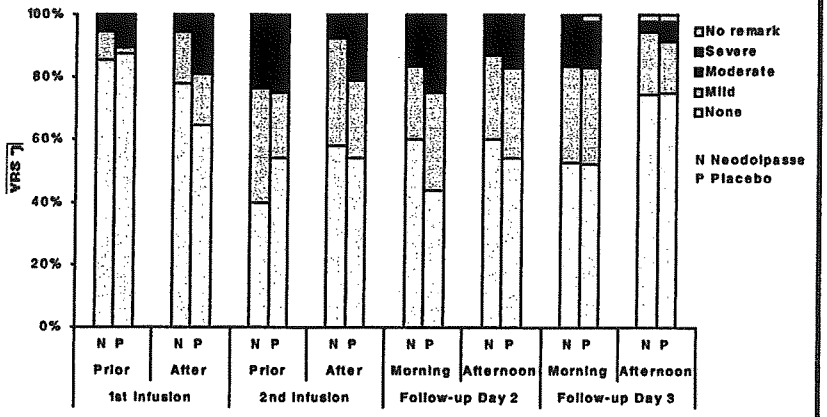
Subjective pain intensity assessed by the VAS did not show any statistically significant differences between treatment groups.

Subjective pain intensity assessed by the VRS was generally low from post-surgery to the afternoon of follow-up Day 3. Similar proportions of patients in both treatment groups rated their pain intensity as none, mild, moderate or severe at the individual observation times.



*) Verbal rating scale
Percentage of patients with no, mild, moderate or severe pain

Subjective pain intensity assessed by the VRS did not show any statistically significant difference between treatment groups.

17/60 patients (28.3%) in the Neodolpasse and 27/60 patients (45.0%) in the placebo group had a fever (body temperature >37.5°C) at any time between prior second infusion and follow-up Day 11. Differences in favour of Neodolpasse® were observed between prior second infusion and follow-up Day 3.

The results of the PP data set showed an even more pronounced reduction in the use of morphine by Neodolpasse® than the results of the FAS.

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Safety results:

All patients in the Neodolpasse group received 2 infusions of 250 ml of study medication. In the placebo group all patients received the first infusion and 57/60 patients (95.0%) received the second infusion of 250 ml of study medication.

In total 75 treatment emergent adverse events (TEAEs) occurred in 39 patients (65.0%) receiving Neodolpasse® and 90 TEAEs occurred in 39 patients (65.0%) receiving placebo. No patient died during the course of this study. Two patients in the placebo group experienced 3 serious TEAEs (bradycardia, cardiac arrest, myocardial infarction). Most frequently reported TEAEs were nausea (24 vs. 20 events), vomiting (9 vs. 10 events) and oedema peripheral (4 vs. 7 events in the Neodolpasse and placebo group). The vast majority of TEAEs were mild (52 vs. 52 events) or moderate (23 vs. 35 events). Two incidences of nausea and one incidence of vomiting in the Neodolpasse as well as one incidence of abdominal pain upper in the placebo group were assessed as possibly related to the study medication. The study drug was discontinued due to skin reaction, blister, rash and pruritus in one patient in the placebo group.

Changes in laboratory parameters from pre-surgery to post-surgery were characterised by decreases in erythrocyte and platelet counts, in haemoglobin, creatinine, calcium and magnesium concentration, in haematocrit, in GGT and AP activity as well as an increase in leukocyte count in both treatment groups.

Changes from pre-surgery to post-surgery	Neodolpasse Mean (SD) median	Placebo Mean (SD) median
Erythrocyte count [T/l]	-0.733 (0.337) -0.820	-0.728 (0.267) -0.765
Haematocrit [%]	-6.44 (2.87) -7.00	-6.61 (2.18) -6.95
Haemoglobin [g/dl]	-2.058 (1.000) -2.250	-2.160 (0.734) -2.300
Platelets [G/l]	-39.5 (38.9) -44.0	-43.7 (28.8) -43.5
Creatinine [mg/dl]	-0.081 (0.112) -0.070	-0.122 (0.139) -0.110
GGT [U/l]	-9.6 (8.7) -7.0	-12.0 (20.4) -6.5
AP [U/l]	-17.3 (11.1) -16.5	-18.2 (8.6) -17.0
Calcium [mmol/l]	-0.208 (0.113) -0.200	-0.256 (0.167) -0.230
Magnesium [mmol/l]	-0.073 (0.088) -0.100	-0.094 (0.087) -0.100
Leukocyte count [G/l]	1.201 (2.128) 0.905	1.326 (2.370) 0.785

The changes in laboratory parameters did not show any relevant differences between treatment groups.

Changes in laboratory parameters from post-surgery to follow-up Day 3 were characterised by decreases in erythrocyte count, haematocrit and

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haemoglobin concentration as well as an increase in CRP concentration in both treatment groups. Creatinine concentration showed a slight decrease in the Neodolpasse and an increase in the placebo group.

Changes from post-surgery to follow-up Day 3	Neodolpasse Mean (SD) median	Placebo Mean (SD) median
Erythrocyte count [T/l]	-0.495 (0.398) -0.555	-0.488 (0.499) -0.500
Haematocrit [%]	-4.51 (3.72) -4.55	-4.44 (4.47) -4.00
Haemoglobin [g/dl]	-1.550 (1.213) -1.800	-1.545 (1.467) -1.600
CRP [mg/dl]	40.938 (69.789) 6.570	63.354 (89.238) 9.020
Creatinine [mg/dl]	-0.011 (0.096) -0.005	0.072 (0.209) 0.040

Except for creatinine, changes in laboratory parameters did not show any relevant differences between treatment groups.

Most prominent changes in vital signs were an increase in systolic blood pressure in the placebo group from prior first infusion to after first infusion and decreases in systolic and diastolic blood pressure in the Neodolpasse group from prior second infusion to after second infusion.

	Neodolpasse Mean (SD) median	Placebo Mean (SD) median
After – prior first infusion		
Systolic blood pressure [mmHg]	0.9 (17.2) 0.0	5.0 (15.1) 3.5
After – prior second infusion		
Systolic blood pressure [mmHg]	-5.1 (12.3) -5.5	1.5 (17.5) 3.0
Diastolic blood pressure [mmHg]	-4.8 (9.4) -3.5	0.7 (9.8) 0.0

Changes in systolic and diastolic blood pressure from prior second infusion to after second infusion showed a relevant difference between groups.

Overall tolerability and safety of study medication was rated as good by the vast majority of patients (Neodolpasse: 59/60 patients (98.3%), placebo: 56/60 patients (93.3%)).

Conclusions:

Neodolpasse® can be used to reduce the demand for morphine via PCA in postoperative analgesic treatment.

Substitution of PCA morphine by Neodolpasse® does not reduce pain relief during postoperative analgesic treatment.

The analgesic effect of Neodolpasse® is accompanied by an antipyretic effect.

The use of Neodolpasse® is safe referring to the occurrence of AEs as well as to changes in laboratory parameters and vital signs.

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Neodolpasse® was well tolerated by the patients.		