Name of Sponsor/Company Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Perfalgan™		
Name of Active Ingredient: paracetamol		

SYNOPSIS

Clinical Study Report for Study CN145010

TITLE OF STUDY: A Phase 4, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Analgesic Efficacy and Safety of Intravenous Paracetamol Versus Placebo in Subjects with Postoperative Pain After Total Hip Arthroplasty

INVESTIGATORS/STUDY CENTERS: Subjects from 5 centers in Spain were screened, but only subjects from 4 centers were randomized.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 25-Apr-2006 **CLINICAL PHASE:** PHASE 4
Study Completion Date: 08-Feb-2008

OBJECTIVES:

Primary objective

To evaluate the analgesic efficacy of 1 g of intravenous (IV) paracetamol (Perfalgan™) versus IV placebo, administered every 6 hours (at T0, T6, T12, and T18), as measured by the 24-hour absolute dose of tramadol (i.e., cumulative dose of tramadol plus equivalent dose of morphine from T0 to T24) in the treatment of postoperative pain following total hip arthroplasty.

Secondary objectives

1. To evaluate the analgesic efficacy of 1 g of Perfalgan compared to placebo, administered every 6 hours, as measured by pain intensity scores and pain intensity differences from baseline (i.e., just before administration of study medication), cumulative doses of tramadol (without equivalent doses of morphine) over each 6-hour interval, number of boluses demanded and number of boluses self-administered by the subject over each 6-hour interval and over the 24-hour period, time elapsed between the first study drug administration (i.e., Perfalgan or placebo) and the tramadol start, total concomitant opioid use (whatever the type and route of administration) over the whole study period (72 hours), and subject's global evaluation of efficacy in the treatment of postoperative pain following total hip arthroplasty over a 24-hour period.
2. To evaluate the general safety of 1 g of Perfalgan compared to placebo, administered every 6 hours, in the treatment of postoperative pain following total hip arthroplasty. The general safety was assessed by adverse event (AE) reporting and by assessing the incidence of postoperative nausea and vomiting (PONV), level of sedation, vital signs, and laboratory values. In addition, the number of subjects requiring anti-emetic medication and the total dose of anti-emetic medication over the 24-hour period was assessed.

Exploratory objective

To evaluate the post-surgery discomfort using a new questionnaire recently validated by psychometric parameters (Results can be found in the body of the clinical study report).

METHODOLOGY:

This was a phase 4, multi-center, randomized, double-blind, placebo-controlled, 2-parallel group study. Subjects who had undergone total hip arthroplasty and who had met the selection criteria were randomized to one of the 2 treatment groups, i.e., i.v. paracetamol or i.v. placebo (1:1). Tramadol patient controlled analgesia (PCA) was used as standardized postoperative analgesia.

Subjects were closely monitored during a 24-hour evaluation period where tramadol and morphine intake, pain intensity scores, and subject's global evaluation of efficacy were assessed. AEs, laboratory values, and the post-surgery discomfort were assessed over a 72-hour period, while the PONV score, level of sedation, number of subjects requiring anti-emetic medication, total dose of anti-emetic medication, and vital signs were assessed over a 24-hour period.

NUMBER OF SUBJECTS (Planned and Analyzed):

Eighty-eight subjects (44 subjects per group) were planned to be treated in the study.

Eighty-six subjects were randomized and assigned to treatment. Forty-one subjects received at least one dose of Perfalgan and 45 subjects received at least one dose of placebo.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Male or female in-patient aged from 18 to 80 years, undergoing total hip arthroplasty.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Immediately after arrival in the postanesthesia care unit (PACU), Perfalgan 1 g was administered as a 15-minute IV infusion 4 times at 6-hour intervals.

Batch number first roll out: 5L08636; Expiry date: 31 October 2007
Batch number second roll out: 7A25241; Expiry date: 30 November 2008

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS:

Immediately after arrival in the PACU, matching placebo of Perfalgan was administered as a 15-minute IV infusion 4 times at 6-hour intervals.

Batch number first roll out: 5L00065; Expiry date: 31 January 2007
Batch number second roll out: 7A29702; Expiry date: 31 July 2008

STANDARDIZED POSTOPERATIVE ANALGESIA:

Tramadol was administered using a PCA device as a standardized postoperative analgesia. Tramadol was started as soon as subjects complained of pain (defined by visual analogue scale [VAS] > 30 mm), and was administered as follows: an initial dose of 1 mg/kg (administered by the site personnel) was followed by PCA self-administered bolus doses of 0.2 mg/kg with lockout times of 10 minutes. The maximum daily dose of tramadol was 400 mg. If the 24-hour cumulative dose of tramadol exceeded the recommended dose of 400 mg/day or when a subject experienced insufficient pain relief after initiation of the PCA tramadol, morphine was utilized.

CRITERIA FOR EVALUATION:

Efficacy:

The primary efficacy variable was the 24-hour absolute dose of tramadol. (i.e., cumulative dose of tramadol plus equivalent dose of morphine from T0 to T24)

The secondary efficacy variables were:

- Cumulative doses of tramadol over the 6-hour intervals: 0 – 6 h, 6 – 12 h, 12 – 18 h, and 18 – 24 h;
- Number of boluses demanded and number of boluses self-administered by the subjects over each 6-hour interval and over the 24-hour period;
- Time elapsed between the first study drug administration (T0) and the tramadol start (defined by the time of administration of the 1 mg/kg initial bolus administered by the site personnel);
- Total concomitant opioid use (whatever the type and route of administration) over the whole study period (72 hours);
- Pain intensity scores (at rest and during mobilization) and pain intensity differences from baseline (at rest) assessed on a 4-point verbal scale (VS) and on a 100-mm VAS scale at regular time intervals;
- Subject's global evaluation of efficacy (4-point VS scale).

Safety:

- Number and percentage of subjects presenting at least one treatment-emergent AE (TEAE). An AE was considered treatment-emergent if it started after administration of the study medication or if it was present before administration and worsened afterwards.
- Incidence of PONV
- Level of sedation (5-point VS scale)
- Number and percentage of subjects requiring anti-emetic medication and the total dose of anti-emetic medication administered from T0 to T24
- Changes from baseline of vital signs
- Changes from baseline of laboratory values

The post-surgery discomfort assessment was an exploratory safety variable.

STATISTICAL CONSIDERATIONS:

Sample size:

A sample size of 41 subjects in each group would provide 80% power to detect a 25% tramadol sparing effect in the Perfalgan group, assuming a coefficient of variation of 40% and a two-sided test at the 5% significance level. A total sample size of 88 subjects was planned to account for an anticipated 5% rate of subjects discontinuing early.

Population:

The intent-to-treat (ITT) population was defined as all randomized subjects who took at least one dose of study drug, analyzed according to the randomized treatment. The per protocol (PP) population comprised all subjects in the ITT population, who did not present any relevant protocol deviation (either before or after treatment administration) that could affect the evaluation of efficacy. The safety population was defined as all randomized subjects who took at least one dose of study drug, analyzed as treated.

Efficacy:

The principal efficacy analysis was performed on the ITT population. Subjects were analyzed as randomized. If the study drug (i.e., Perfalgan or placebo) was discontinued between T0 and T24, the efficacy parameters were analyzed using all available data for this population.

A supportive efficacy analysis based on the PP population was carried out if more than 5% of the subjects of the ITT population had relevant protocol deviations. Since the discontinuation of study drug administration was defined as a relevant protocol deviation, subjects that discontinued the study drug were not included in the PP population.

Primary efficacy variable:

The 24-hour absolute dose of tramadol in the two treatment arms of the study was compared using a 1-way analysis of covariance (ANCOVA) model including a 2-level treatment effect, and gender, center, and baseline pain intensity rated on the VAS scale as covariates. A two-sided 95% confidence interval was calculated using the least square means and root mean square error (RMSE) of the ANCOVA model. Secondary, an interactive ANCOVA model including in addition treatment-by-gender and treatment-by-baseline pain intensity interactions was performed to explore heterogeneity of treatment effect across gender and baseline levels.

The normality assumption underlying the ANCOVA was checked. If this assumption was not supported by the data (p-value < 0.01 for the Shapiro-Wilk test of Normality), the results of the Van Elteren's extension to the Wilcoxon test, stratified by baseline pain intensity (VS scale) and gender, were reported instead of the ANCOVA results, except when the non-parametric test led to the same conclusion as the ANCOVA model for both the principal and supportive analysis. The median 24-hour absolute dose of tramadol was calculated in each treatment group and the Hodges-Lehman estimate of the median difference was calculated with its associated 95% confidence interval.

Secondary efficacy parameters:

The same methodology as that used for the primary variable was used for quantitative data (cumulative doses of tramadol over the 6-hour intervals, number of boluses demanded and number of boluses self-administered by subjects over each 6-hour interval and over the 24-hour period, pain intensity scores).

The Gehan-Wilcoxon test stratified by baseline pain intensity (VS scale) and gender was used for survival type data. The percentiles of the survival distribution were calculated using the Kaplan-Meier product limit estimator. The median times and the 95% confidence interval were produced. In addition, the hazard ratio with 95% confidence interval was provided using Cox regression with baseline pain intensity (VS scale) and gender as covariates.

The Cochran-Mantel-Haenszel test with modified ridit scores (i.e., Van Elteren test) stratified by baseline pain intensity (VS scale) and gender was used for ordered categorical data and for binary data. The medians were calculated for each treatment group and the Hodges-Lehman estimate of the median difference was calculated with its associated 95% confidence interval.

A Fisher's exact test was provided for the number of subjects requiring opioids from T0 to T72.

Safety analyses:

Safety analyses were performed on the safety population. Subjects were analyzed according to the actual treatment received. Results were reported during the treatment (and follow-up) phase. These phases were defined as follows:

- Treatment phase: from T0 (initiation of study therapy [Perfalgan or placebo]) to T24 (i.e., 6 hours after last administration of study drugs);
- Follow-up phase: from T24 to T72 (i.e., 72 hours after the first dose of study drugs).

The number of subjects having a TEAE and the number of subjects requiring anti-emetic medication was compared between the Perfalgan and placebo group using the Fisher's exact test and odds ratio with 95% confidence interval. The dose of anti-emetic medication administered was only listed.

For laboratory tests, changes from baseline were calculated for each treatment group at the follow-up visit. In addition, crosstabulations of the incidence of clinically relevant out-of-range laboratory values at follow-up versus the baseline values were presented.

For vital signs, a two-sided Wilcoxon signed rank test was performed to evaluate the changes from baseline at all time points assessed for each treatment group.

The medians of the PONV scores and sedation levels were calculated at all assessed time points for each treatment group and the changes from baseline were evaluated using a two-sided Wilcoxon signed rank test. The Van Elteren test stratified by baseline pain intensity (VS scale) and gender was used to compare the two treatment arms and the Hodges-Lehman estimate of the median difference was calculated with its associated 95% confidence interval. The worst score on PONV over time was also determined for both treatment groups.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographics Characteristics:

Eighty-six subjects were randomized and received at least one dose of study medication (41 Perfalgan and 45 placebo). Thirteen subjects were screened but never randomized. Seventy-nine subjects completed the study (40 from the Perfalgan group and 39 from the placebo group). Six subjects (1 subject from the Perfalgan group and 5 subjects from the placebo group) discontinued the study medication prematurely. The reasons for early discontinuation of treatment were AEs (reported for 1 subject from the Perfalgan group and 3 subjects from the placebo group) and protocol deviations (reported for 2 subjects from the placebo group). One subject from the placebo group received all four doses of study medication, but discontinued the study before T24 due to an AE.

The safety and ITT population consisted of 41 subjects in the Perfalgan group and 45 subjects in the placebo group. Several subjects had relevant protocol deviations (including 1 subject in the Perfalgan group and 5 subjects in the placebo group who discontinued the study drug). This resulted in a PP population consisting of 61 subjects (34 subjects in the Perfalgan group and 27 subjects in the placebo group).

Demographic characteristics were similar in both treatment groups for the ITT as well as for the PP population, except that the proportion of female subjects was slightly higher in the Perfalgan group than in the placebo group (**Table 1**). The distribution of subjects over the centers was similar in both treatment groups.

Table 1: Baseline Demographic Characteristics

	ITT Population		PP Population	
	Perfalgan (N = 41)	**Placebo (N = 45)**	**Perfalgan (N = 34)**	**Placebo (N = 27)**
Age (years)				
Mean ± SE	68.3 ± 1.44	67.5 ± 1.50	68.6 ± 1.58	69.1 ± 1.90
Height (cm)				
Mean ± SE	162.7 ± 1.50	162.2 ± 1.51	162.1 ± 1.52	161.3 ± 1.94
Weight (kg)				
Mean ± SE	74.9 ± 1.79	74.6 ± 1.88	73.3 ± 1.76	73.3 ± 2.33
BMI (kg/m^2)				
Mean ± SE	28.2 ± 0.44	28.5 ± 0.61	27.9 ± 0.48	28.3 ± 0.71
Gender, n (%)				
Female	23 (56.1)	19 (42.2)	20 (58.8)	12 (44.4)
Male	18 (43.9)	26 (57.8)	14 (41.2)	15 (55.6)
Race, n (%)				
Caucasian	40 (97.6)	45 (100.0)	33 (97.1)	27 (100.0)
Other	1 (2.4)	0	1 (2.9)	0

N: number of subjects with data, n: number of subjects with observation
Source: Table 14.1 D

Efficacy Results:

The primary efficacy endpoint was the 24-hour absolute dose of tramadol (i.e., cumulative dose of tramadol plus equivalent dose of morphine from T0 to T24). The principal analysis (on the ITT population) revealed that after adjusting for the effects of gender, center, and baseline pain intensity score (VAS scale), there was no statistically significant difference between Perfalgan and placebo treatment in the 24-hour absolute dose of tramadol administered (see Table 2). This result was supported by the analysis on the PP population.

Table 2: 24-Hour Absolute Dose of Tramadol

	Perfalgan		Placebo		Perfalgan – Placebo	
Dose (mg) [a]	**N**	**Least square mean ± SE**	**N**	**Least square mean ± SE**	**Least square mean difference (95% CI)**	**p-value**
ITT population	41	335.1 ± 36.65	44[b]	322.1 ± 36.09	12.9 (-84.6; 110.5)	0.792
PP population	34	271.0 ± 37.56	26[b]	327.3 ± 42.33	-56.3 (-157.9; 45.2)	0.271

N: number of subjects with data
[a] Evaluated using ANCOVA model including a 2-level treatment effect, and gender, center, and baseline pain intensity rated on the VAS scale as covariates.
[b] One subject was excluded from the ANCOVA, because she had no baseline pain intensity value (VAS scale).
Source: Table 14.2 A and Table 14.2 B

Regarding the secondary efficacy endpoints, the principal analysis revealed that there was no statistically significant difference between the Perfalgan and placebo group for the cumulative doses of tramadol over the 6-hour intervals, the number of boluses demanded and the number of boluses self-administered by the subjects over the 24-hour period and over the 6-hour intervals, the total concomitant opioid use, the changes in pain intensity scores assessed at rest on a 4-point VS and on a 100-mm VAS scale, the pain

intensity scores assessed during movement on a 100-mm VAS scale, and the subject's global evaluation of efficacy of the treatment.

In contrast, the time to first administration of tramadol was statistically significantly longer for subjects treated with Perfalgan than for subjects treated with placebo (p-value = 0.012 in the ITT population). The median (95% CI) time to first administration was 1.27 hours (1.00; 1.75) in the Perfalgan group and 1.00 hour (0.65; 1.25) in the placebo group.

In general, the results were supported by the analysis on the PP population.

Safety Results:

There were no deaths. Two subjects (both receiving placebo) experienced at least one serious AE (SAE) during the treatment phase. One subject experienced severe joint dislocationbradycardia and severe hypotension, while the other subject experienced severe bradycardia and severe hypotension. The former subject completed treatment with thejoint dislocation. These subjects discontinued the study or study drug, but discontinued the study before T24 due to the joint dislocation SAE. The latter subject discontinued the study medication due to thethese SAEs, bradycardia and hypotension. In addition, three3 more subjects discontinued the study drug treatment due to AEs. In (one in the Perfalgan group, one and 2 in the placebo group). The former subject discontinued the study drug due to severe pain. In, while the placebo group, one subjectlatter 2 subjects discontinued the study drug due to mild syncope and one due to severe agitation.

During the treatment phase, TEAEs were experienced by 32 subjects (78%) receiving Perfalgan and 35 subjects (78%) receiving placebo. During the follow-up phase, TEAEs were reported for 17 (43%) and 16 (40%) subjects, respectively. The number of subjects having a TEAE was not statistically significantly different in the Perfalgan group compared to the placebo group.

The summary of AEs is presented in Table 3.

Table 3: Summary of AEs

	Perfalgan (N = 41)	**Placebo (N = 45)**
Death	0	0
SAE	0	2 (4.4)
Adverse events leading to discontinuation	1 (2.4)	3 (6.7)
Pain	1 (2.4)	0
Bradycardia	0	1 (2.2)
Syncope	0	1 (2.2)
Agitation	0	1 (2.2)
Hypotension	0	1 (2.2)
Most frequently reported AEs[1] and AEs of interest. Any adverse event during the treatment phase of the study drug	32 (78.0)	35 (77.8)
Nausea	21 (51.2)	21 (46.7)
Vomiting	8 (19.5)	6 (13.3)
Urinary retention	7 (17.1)	2 (4.4)
Anemia postoperative	6 (14.6)	2 (4.4)
Hypotension	5 (12.2)	7 (15.6)
Pyrexia	1 (2.4)	6 (13.3)
Syncope vasovagal	2 (4.9)	5 (11.1)
Bradycardia	2 (4.9)	3 (6.7)
Pain	2 (4.9)	1 (2.2)
Malaise	2 (4.9)	1 (2.2)
Constipation	2 (4.9)	0
Hypertension	0	2 (4.4)
Any adverse event during the follow-up phase	17 (42.5)	16 (40.0)
Anemia postoperative	4 (10.0)	3 (7.5)
Pyrexia	4 (10.0)	1 (2.5)
Constipation	2 (5.0)	2 (5.0)
Nausea	2 (5.0)	1 (2.5)
Insomnia	2 (5.0)	1 (2.5)
Hypotension	1 (2.5)	2 (5.0)
Diarrhea	1 (2.5)	2 (5.0)
Hypertension	1 (2.5)	0
Disorientation	0	2 (5.0)
Abdominal distension	0	1 (2.5)

N: number of subjects with data

[1] Most frequently AEs are those reported for at least 5% of the subjects in any treatment group during the treatment or follow-up phase.

Source: Table 14.3 A and Table 14.3 B

Severe TEAEs only occurred during the treatment phase. In this phase, 4 subjects (10%) from the Perfalgan group and 6 subjects (13%) from the placebo group experienced severe AEs.

AEs considered treatment-related according to the investigator were reported for 18 subjects (9 in each treatment group) during the treatment phase. The most frequent treatment-related AEs were nausea (reported for 20% and 9% of the subjects in the Perfalgan and placebo group, respectively) and vomiting (reported for 5% and 7%). During the follow-up phase, one AE considered treatment-related was reported for 1 subject from the Perfalgan group.

Laboratory values and their changes from baseline were, in general, similar in the Perfalgan and placebo group. The most frequent treatment-emergent out-of-range laboratory values at the follow-up visit (reported in more than 10% of the subjects in any treatment group) were usually reported less often in the Perfalgan than in the placebo group. The incidence in the Perfalgan group was at least 10% lower than in the placebo group for hemoglobin, gamma-glutamyltransferase (GGT), and red blood cells (RBCs). For phosphorus, a difference in incidence higher than 10% was also observed, but for this parameter, the incidence was higher in the Perfalgan than in the placebo group.

The values for all vital signs and their changes from baseline were, in general, similar for both treatment groups at all time points assessed.

There were no statistically significant differences between the Perfalgan and placebo group in PONV scores, worst PONV score over time, sedation level, and number of subjects requiring anti-emetic medication.

CONCLUSIONS:

- There was no statistically significant difference between the analgesic efficacy of 1 g of Perfalgan versus placebo, administered every 6 hours, as measured by the 24-hour absolute dose of tramadol, after adjusting for the effects of gender, center, and baseline pain intensity score (VAS scale).
- No statistically significant differences between the two treatments were seen, except for the time to first administration of tramadol, which was statistically significantly longer for subjects treated with Perfalgan than for those treated with placebo.
- Overall, the number and percentage of subjects presenting at least one TEAE were similar in the Perfalgan and placebo group. In addition, there was no statistically significant difference between the Perfalgan and placebo group in incidence of postoperative nausea and vomiting, level of sedation, and number of subjects requiring anti-emetic medication. Changes from baseline of vital signs and laboratory values were similar in the two treatment groups. The most frequent treatment-emergent out-of-range laboratory values were usually reported less often in the Perfalgan than in the placebo group.

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