1. TITLE PAGE

Study title	Prospective, monocentric, controlled, randomized, double-blind study to compare two different propofol emulsions regarding tolerability and injection pain during the induction of anesthesia in adults
Name of test drug / investigational product	Propofol MCT / LCT 0.5% (Propofol-®Lipuro 0.5%) and Propofol MCT / LCT 1.0% (Propofol-®Lipuro 1%)
Indication studied	Anesthesia induction
Study design	Prospective, monocentric, controlled, randomized, double-blind parallel-group study
Sponsor	B. Braun Melsungen AG Division Hospital Care Center of Excellence Pharmaceuticals Carl-Braun-Straße 1 34212 Melsungen, Germany
Study number	HC-G-H-0705
EudraCT number	2007-003571-39
Development phase of study	Phase III
Study initiation date	First patient in : 07.05.2008
Study completion date	Last patient out: 24.09.2008
Principal investigator (Leiter der klinischen Prüfung according to German Drug Law)	Dr. med. S. Soltész Oberarzt der Klinik für Anästhesie und operative Intensivmedizin Klinikum Leverkusen gGmbH Am Gesundheitspark 11 51375 Leverkusen, Germany

Study coordinator	[redacted] Senior Scientific Manager B. Braun Melsungen AG Division Hospital Care Center of Excellence Pharmaceuticals Carl-Braun-Straße 1 34212 Melsungen, Germany
GCP	This study was performed in compliance with ICH Good Clinical Practice (GCP) (CPMP/ICH/135/95).
Date of the report	15.09.2009

2. SYNOPSIS

Name of sponsor	B. Braun Melsungen AG, Carl-Braun-Straße 1, 34212 Melsungen, Germany
Name of finished product	Propofol-®Lipuro 0.5% and Propofol-®Lipuro 1%[1]
Name of active ingredient	Propofol
Study title	Prospective, monocentric, controlled, randomized, double-blind study to compare two different propofol emulsions regarding tolerability and injection pain during the induction of anesthesia in adults
Investigators	• Dr. med. S. Soltész Oberarzt der Klinik für Anästhesie und operative Intensivmedizin Klinikum Leverkusen gGmbH Am Gesundheitspark 11, 51375 Leverkusen, Germany • [redacted] Klinikum Leverkusen gGmbH Am Gesundheitspark 11, 51375 Leverkusen, Germany • [redacted] Klinikum Leverkusen gGmbH Am Gesundheitspark 11, 51375 Leverkusen, Germany • [redacted] Klinikum Leverkusen gGmbH Am Gesundheitspark 11, 51375 Leverkusen, Germany
Study center	Klinikum Leverkusen gGmbH Am Gesundheitspark 11, 51375 Leverkusen, Germany
Publication (reference)	–
Study period	Date of first patient enrolled : 07.05.2008 Date of last patient completed : 24.09.2008
Phase of development	III
Objectives	Primary objective: To demonstrate better venous tolerability of diluted propofol compared to undiluted propofol (reduction of injection pain during anesthesia induction). Secondary objective: Collection of data regarding hemodynamics, propofol dosage, need of propofol, level of triglycerides as well as data regarding surgery, injection pain, concomitant medication, postoperative examination of the venous punction site, but also all adverse events occurring during the course of the clinical study.
Methodology	Prospective, monocentric, controlled, randomized, double-blind, **'observer blind'**, clinical phase III study
Number of patients	• Planned for enrolment : N=100 (50 per group) • Enrolled and randomized : N=100 (50 per group) • Safety population : N=100 (50 / 50)* • Intention-to treat set : N=100 (50 / 50)* • Per protocol set : N=100 (50 / 50)* [*: Propofol 0.5% / Propofol 1.0%]
Diagnosis and main criteria for inclusion	Male and female adults aged 18 to 80 years undergoing elective surgery and general anesthesia: • ASA classification I – III • Venous access for induction of anesthesia situated on the dorsum of the hand.

[1] short: Propofol 0.5%, Propofol 1%

Test product	Propofol MCT / LCT 0.5% (Propofol-®Lipuro 0.5%)
Dose	Bolus 2 mg/kg i.v. over 60 sec, if required by steps additionally 0.5 mg/kg i.v. over 15 sec until absence of winking reflex
Mode of administration	i.v. boli over 60 sec (initial) and 15 sec
Batch no.	7143C52
Duration of treatment	Anesthesia induction over a period of approximately 5 minutes
Reference product	Propofol MCT / LCT 1.0% (Propofol-®Lipuro 1%)
Dose	Bolus 2 mg/kg i.v. over 60 sec, if required by steps additionally 0.5 mg/kg i.v. over 15 sec until absence of winking reflex
Mode of administration	i.v. boli over 60 sec (initial) and 15 sec
Batch no.	7475C33
Criteria for evaluation	
Efficacy	• Need of propofol. • Time until absence of winking reflex.
Safety	• **Primary endpoint:** 1st primary endpoint: Incidence of spontaneous expression of injection pain; 2nd primary endpoint: Total pain incidence (spontaneous pain reactions and/or positive rating of the pain VAS). • Type of spontaneous pain reactions. • Assessment of pain VAS 5, 20, and 35 sec after 1st propofol injection - VAS 0 : no pain - VAS 1 – 3 : mild pain - VAS 4 – 6 : moderate pain - VAS 7 – 10 : severe pain. • Postoperative (3 – 6 h after extubation) assessment of injection pain by means of VAS. • Postoperative (3 – 6 h after extubation) assessment of patient's satisfaction with anesthesia induction. To this end, the patients gave school grades from 1 to 6. • Triglyceride levels before anesthesia induction (baseline), and 3 and 20 minutes after end of anesthesia induction. • Safety parameters during anesthesia induction and maintenance: - blood pressure - heart rate - arterial oxygen saturation. • Concomitant treatment during surgery until the end of observation. • Postoperative examination of the venous punction site. • Adverse events and adverse drug reactions during the entire course of the study.
Statistical methods	• χ^2 test • U test • t-test • analysis of variance (ANOVA) • analysis of covariance (ANCOVA) • significance level α=0.05 two-tailed.

Efficacy results

➢ Time to absence of winking reflex (U test: p=0.8365)

- Propofol 0.5% : 1.38 ± 0.38 min
- Propofol 1.0% : 1.44 ± 0.45 min.

➢ Propofol required until absence of winking reflex [mg] (U test: p=0.7277)

- Propofol 0.5% : 179.6 ± 30.1 mg
- Propofol 1.0% : 189.4 ± 49.1 mg.

➢ Propofol required until absence of winking reflex [mg/kg] (U test: p=0.1203)

- Propofol 0.5% : 2.19 ± 0.25 mg/kg
- Propofol 1.0% : 2.28 ± 0.31 mg/kg.

Safety results

➢ 1st primary endpoint: Incidence of spontaneous expression of injection pain (χ^2 test: p=0.0270)

- Propofol 0.5% : N=1 (2.0%)
- Propofol 1.0% : N=7 (14.0%).

➢ Maximum pain VAS 5, 20, and 35 sec after initial anesthesia induction (U test: p=0.0064)

Intensity	Propofol 0.5%	Propofol 1.0%
no pain	27 (54.0%)	18 (36.0%)
mild pain	19 (38.0%)	14 (28.0%)
moderate pain	3 (6.0%)	13 (26.0%)
severe pain	1 (2.0%)	5 (10.0%)

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➢ Time of maximum pain after initial anesthesia induction (Propofol 0.5%: N=23; Propofol 1.0%: N=32)

Time*	Propofol 0.5%	Propofol 1.0%
5 sec	6 (26.1%)	1 (3.1%)
20 sec	2 (8.7%)	10 (31.3%)
35 sec	15 (65.2%)	21 (65.6%)

[*: earliest time of maximum pain].

➢ Incidence of moderate to severe pain at the maximum pain VAS 5, 20, and 35 sec after initial anesthesia induction (χ^2 test: p=0.0007)

- Propofol 0.5% : N= 4 (8.0%)
- Propofol 1.0% : N=18 (36.0%).

➢ 2nd primary endpoint: Total pain incidence (χ^2 test: p=0.0440)

- Propofol 0.5% : N=23 (46.0%)
- Propofol 1.0% : N=33 (66.0%).

➢ Distribution of the pain VAS 5, 20, and 35 sec after initial propofol injection:

Stat. estimate	Propofol 0.5%			Propofol 1.0%		
	5 sec	20 sec	35 sec*	5 sec	20 sec	35 sec*
minimum	0	0	0	0	0	0
1st quartile	0.00	0.00	0.00	0.00	0.00	0.00
2nd quartile	0.00	0.00	0.00	0.00	2.00	2.50
3rd quartile	0.00	1.00	2.00	0.00	3.00	5.00
maximum	3	3	7	7	10	10
mean	0.28	0.46	1.00	0.46	1.90	2.78
standard dev.	0.67	0.84	1.48	1.27	2.31	2.89

[*: last observation carried forward;
U test: p=0.8976 / 0.0002 / 0.0027 after 5 / 20 / 35 sec].

➢ Distribution of the maximum pain VAS after initial propofol injection:

Stat. estimate	Propofol 0.5%	Propofol 1.0%
minimum	0	0
1st quartile	0.00	0.00
2nd quartile	0.00	3.00
3rd quartile	2.00	5.00
maximum	7	10
mean	1.00	2.88
standard dev.	1.48	2.95

[U test: p=0.0013].

➢ Hypertriglyceridemia (i.e. triglycerides > 200 mg/dL) was the only adverse event (except for injection pain) which was classified as related to the study medication (i.e. adverse drug reaction). The incidence was (χ^2 test: p<0.0001)

- Propofol 0.5% : N=44 (88.0%)
- Propofol 1.0% : N=26 (52.0%).

➢ Triglycerides (mg/dL; raw data): Means and standard deviations (ranges) of the triglycerides worked out as follows:

Time of measurement	Propofol 0.5%	Propofol 1.0%	p-value
before anesthesia induction	132.7 ± 60.5 (42 – 296)	155.3 ± 84.1 (51 – 401)	0.1282
end of anesthesia induction + 3 min	284.4 ± 75.0 (124 – 448)	239.3 ± 91.6 (128 – 492)	0.0087
end of anesthesia induction + 20 min	182.1 ± 72.1 (64 – 364)	176.2 ± 86.4 (68 – 409)	0.7143

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➢ Triglycerides (mg/dL; baseline adjusted): A significantly higher increase of the triglycerides was recorded 3 min after end of anesthesia induction, resulting in an overall higher level in the Propofol 0.5% study group. 20 min after end of anesthesia induction, the differences between both groups were markedly decreased, but still significant. The baseline-adjusted mean levels (± SEM) were distributed as follows:

Time of measurement	Propofol 0.5%	Propofol 1.0%	p-value
before anesthesia induction	143.4	143.4	
end of anesthesia induction + 3 min	296.6 ± 4.8	228.2 ± 4.8	<0.0001
end of anesthesia induction + 20 min	193.2 ± 4.8	164.7 ± 4.8	<0.0001

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➢ Blood pressure and heart rate: In the entire course of measurements no significant group differences were seen for blood pressure and heart rate. Especially, no statistically significant differences were seen after anesthesia induction between Propofol 0.5% and Propofol 1.0% with regard to changes from baseline in blood pressure and heart rate.

➢ Interactions of treatment and injection pain were detected for DBP, MAP, and heart rate:

- in study group Propofol 0.5% higher levels of DBP, MAP, and heart rate were seen in patients with injection pain as compared to patients without injection pain
- in study group Propofol 1.0% lower levels of DBP, MAP, and heart rate were seen in patients with injection pain as compared to patients without injection pain.

➢ Oxygen saturation: No statistically significant differences between the study groups were detected in respect to the oxygen saturation.

➢ Patient satisfaction with anesthesia induction: A slight tendency in favor of Propofol 0.5% in comparison with Propofol 1.0% was determined (U test: p=0.1594):

Patient satisfaction	Propofol 0.5%	Propofol 1.0%
very good	7 (14.0%)	7 (14.0%)
good	42 (84.0%)	35 (70.0%)
satisfactory	1 (2.0%)	8 (16.0%)
adequate	–	–
inadequate	–	–
insufficient	–	–

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Conclusions

Efficacy

Concerning the need of propofol, results in both groups are similar. The time until absence of winking reflex was 1.38 ± 0.38 min in the Propofol 0.5% and 1.44 ± 0.45 min in the Propofol 1.0% group. The amount of propofol required until absence of winking reflex came to 179.6 ± 30.1 mg in the Propofol 0.5% and 189.4 ± 49.1 mg in the Propofol 1.0% group. Further surgery-induced medication was also homogeneously distributed in both study groups. In total, there is no difference, neither statistically nor clinically, in the course of anesthesia in the study groups Propofol 0.5% and Propofol 1.0%.

Safety

Injection pain – primary endpoint:

Injection pain was differently distributed in the two study groups with clear advantages for Propofol 0.5%. The rate of spontaneous expression of injection pain was much lower in the Propofol 0.5% group (1 out of 50 patients) compared to the Propofol 1.0% group (7 out of 50 patients). The difference was statistically significant (χ^2 test: p=0.0270; 1st primary endpoint). The type of reaction was: grimacing (Propofol 0.5%: n=1; Propofol 1.0%: n=4), drawing back the arm (Propofol 1.0%: n=1), and verbal reactions (Propofol 1.0%: n=2).

The assessment of the pain VAS 5, 20, and 35 sec after initial injection yielded significant advantages in favor of Propofol 0.5% after 20 (p=0.0002) and 35 sec (observed cases: p=0.0006; last observation carried forward: p=0.0027). The maximum pain intensity immediately after injection was distributed as follows (p=0.0064):

Intensity	VAS	Propofol 0.5%	Propofol 1.0%
no pain	0	27 (54.0%)	18 (36.0%)
mild pain	1 – 3	19 (38.0%)	14 (28.0%)
moderate pain	4 – 6	3 (6.0%)	13 (26.0%)
severe pain	7 – 10	1 (2.0%)	5 (10.0%)

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A marked discrimination was especially seen for moderate to severe pain. The rates were 8.0% in the Propofol 0.5% and 36.0% in the Propofol 1.0% group (χ^2 test: p=0.0007). The total pain incidence amounted to 46.0% in the Propofol 0.5% and 66.0% in the Propofol 1.0% group (χ^2 test: p=0.0440; 2nd primary endpoint).

Hypertriglyceridemia:

Due to the fact that the administered Propofol is diluted in a lipid emulsion, the triglyceride levels were increased especially in the Propofol 0.5% study group three minutes after anesthesia induction due to the absolute higher amount of fat emulsion administered with this preparation. Twenty minutes after Propofol treatment, however, a clear decreasing tendency was observed, but the levels were still somewhat higher than baseline values especially in the Propofol 0.5% group. Thus, the increase in triglycerides seems to be only temporary. Apart from injection pain, hypertriglyceridemia was the only adverse event which was classified as related to the study medication, i.e. an adverse drug reaction. The incidences were 88.0% (Propofol 0.5%) and 52.0% (Propofol 1.0%), respectively.

Hemodynamics:

In the entire course of measurements no clinically relevant differences were seen for blood pressure and heart rate. A slight interaction of treatment and injection pain with regard to DBP, MAP, and heart rate must be regarded as artifact.

Summary

In summary it is demonstrated in this study that the frequency and intensity of injection pain are lower under Propofol 0.5% administration compared to Propofol 1.0% in adults undergoing elective surgery under general anesthesia. Particularly the incidence of moderate to severe pain could markedly be reduced from 36.0% to 8.0%. Furthermore it was shown that time and amount of propofol needed until absence of winking reflex were identical for Propofol 0.5% and 1.0%.

As expected for bolus injection the increase of the triglyceride levels can be concluded as transient. In both groups the triglyceride levels reached peak levels three minutes after induction of anesthesia, followed by an immediate decline of the triglyceride levels within 20 minutes.

Based upon these results Propofol 0.5% is a valuable alternative to Propofol 1.0% to be used in adults for induction of anesthesia in order to reduce frequency of injection pain and to lower pain intensity.