Synopsis Final Clinical Study Report for Study Etoricoxib fast-track
(ICH Topic E 3 Structure and Content of Clinical Study Reports)

1a) Name of Sponsor	Charité - Universitätsmedizin Berlin Campus Charité Mitte Charitéplatz 1 10117 Berlin Germany Tel.: 030-450 570 142 Fax: 030-450 570 914
1b) Name of Sponsor-Investigator	Univ.-Prof. Dr. med. C. Spies Department of Anesthesiology and Intensive Care Medicine Campus Charité Mitte and Campus Virchow - Klinikum Charité - Universitätsmedizin Berlin Augustenburger Platz 1 13353 Berlin Germany Tel.: 030-450 551001 Fax: 030-450 551909 claudia.spies@charite.de
2) Name of finished product	1. Arcoxia® capsule 120 mg/d for 6 days, ATC code: M01AH05 MA number: 59863.02.00 2. P-Tabletten weiß 8 mm Lichtenstein for 6 days, ATC code: V03AX MA number: 6927122.00.00
3) Name of active substance	Blinding of Verum and Placebo was supplied by the method of over-encapsulation by Empty Hard Gelatin Capsules (Swedish ORANGE PAQUE). Dosage form: orange-red gelatine capsules size DB AA Customer: Capsugel NV; product Name: HGC AADB 22.307/22.307 Product Code: 0011674 capsugel Lot number. 70267881 Name of excipients: Gelatin, Red Iron Oxide, Titanium dioxide 1 capsule contains capsule filler according to DAC/NRF (Deutsche Arzneimittel-Codex® /Neue Rezeptur Formularium) 2001: mannitol and highly dispersed silicon dioxide and either active substance 1 (Verum) or 2 (Placebo): <u>Ad 1. Arcoxia® 120 mg:</u> Active substance: 120 mg Etoricoxib *Further ingredients:* *Core:* Calcium hydrogen phosphate (anhydrous) Croscarmellose sodium Magnesium stearate Microcrystalline cellulose

	Tablet coating: Carnauba wax Lactose monohydrate 5,6 mg Hypromellose Titanium dioxide (E171) Triacetin Indigo carmine lake (E132) Yellow ferric oxide (E172) <u>Ad 2. P-Tabletten weiß 8 mm Lichtenstein®:</u> Active substance: none Further ingeredients cellulose powder, lactose monohydrate magnesium starate, microcrystallin cellulose
5) Title of study (according to EudraCT)	A double-blind, randomized, placebo controlled study to evaluate the effectiveness of etoricoxib as an additive analgesic to epidural analgesia in colon or rectum fast-track surgery Eine doppelblinde, randomisierte, placebokontrollierte Studie zur Bewertung der Effektivität von Etoricoxib als zusätzliches Analgetikum zur Epiduralanästhesie bei fast-track Kolon-oder Rektumchirurgie Code number: Etoricoxib fast-track Eudra-CT No: 2010-021604-16 Clinicaltrials.gov: NCT01259830 EudraCT-Number of the protocol: 2008-006135-12 BfArM approval: Date of approval: 24.11.2010 (Protocol V1.1) Number: 4036727 1. Amendment Protocol V1.2: 23.09.2011 2. Amendment new SMPC Arcoxia 03/2013 04.07.2013 Ethical approval: Date of approval: 08.12.2010 (with conditions) 23.12.2010 (conditions met) (Protocol V1.1) 1. Amendment Protocol V1.2: 14.09.2011 2. Amendment reevaluation study centers Charité and Lichtenberg 10.05.2013, new study center Minden 10.05.2013 3. Amendment study center St. Hedwig 11.06.2013 4. Amendment new SMPC Arcoxia 03/2013 21.06.2013

Date	Amendment
18.12.2010	Amendment changes of the protocol 01 to 02 within the ethical applications
23.09.2011	Substantial Amendment 01: Primary reason for amendment were changes in study design: one inclusion criterion “realization of planned colon or rectum surgery in the fast track design after clinical standards including an epidural catheter” was specified. One secondary endpoint was added: length of ICU stay. The time schedule of the study was adapted.and minimal changes of the summary of product characteristics Arcoxia 01/2011 regarding

	updated side effects were included in the new protocol version and patient information sheets.The
10.05.2013	Amendment 02 Ethics commission: reevaluation of the study center 1 Charité and 2 Lichtenberg in Berlin, new study center 3 Minden
11.06.2013	Amendment 03 Ethics commission: study center 4 St. Hedwig
21.06.2013	Amendment 02 BfArM/Amendment 04 Ethics commission: new SMPC Arcoxia 03/2013

Recruitment stop on 29.03.2014 after inclusion of 81 patients in all trial centres because of logistical/financial reasons.

Premature termination of the clinical trial for logistic / financial reasons in all participating trial centers. The termination was not due to security concerns.

6) Investigators

1) Charité- University Medicine Berlin (Berlin)

Coordinating Investigator (Leiter der klinischen Prüfung):
Univ.-Prof. Dr. med. Claudia Spies
Department of Anesthesiology and Intensive Care Medicine
Campus Charité Mitte and Campus Virchow - Klinikum
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany
Tel.: +49 30-450 551001
Fax: +49 30-450 551909
E-Mail: Claudia.Spies@charite.de

Authorized Representative Investigator
OA Dr. med. Torsten Beutlhauser
Department of Anesthesiology and Intensive Care Medicine
Campus Charité Mitte and Campus Virchow - Klinikum
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Germany

Investigators:
Dr. med. Anika Müller
Dr. med. Friedrich Borchers
Dr. med. Micco Jacoby
Dr. med. Nicolai Netzhammer
Dr. Jan Baars
Dr. med. Ulrike Haase
OA Dr. med. Thomas Fritzsche
OA Dr. med. Finn Radtke
OÄ Dr. med. Anke Hübner
Dr. med. Christina West
Dr. med. Daniel Panne
Dr. med. Anton Goldmann
Dr. med. Katharina Chalk

	(previously Katharina Berger) Juliane Rau Prof. Dr. med. Schäfer Dr. med. Joachim Gerst Lars Scholz OÄ Dr. med. Manuela Keitel Prof. Dr. med. Sander Ruta Kasperiunaite Dr. med. Tobias Moormann Dr. med. Mathieu Duquesne Dr. med. Michael Krüger Dr. med. Franziska Gilg 2) Sana Klinikum Lichtenberg (Berlin) **Principal investigator:** Dr. med. Yvonne Tock Sana Klinikum Lichtenberg, Oskar-Ziethen-Krankenhaus Department of Anesthesiology Fanningerstraße 32, 10365 Berlin Tel.: +49 30 55 18 2360/76 Fax.: +49 30 55 18 2399 E-Mail: yvonne.tock@sana-kl.de **Authorized Representative investigator** Dipl. Inf. Uwe Trebus Sana Klinikum Lichtenberg, Oskar-Ziethen-Krankenhaus Department of Anesthesiology Fanningerstraße 32, 10365 Berlin Investigators: Dr. Lars-Olav Harnisch Mirco Wolf Dr. med. Micco Jacoby Dr. med. Nicolai Netzhammer 3) St. Hedwig clinic (Berlin) **Principal investigator:** OÄ Brit Schill St. Hedwig Kliniken Berlin GmbH Department of Anesthesiology and Intensive Care Medicine Große Hamburger Straße 5-11 10115 Berlin Germany Tel: +49 30 23 11- 0 Fax: +49 30 23 11 - 24 22 E-Mail: b.schill@alexius.de **Authorized Representative investigator** Dr. med. Martin Franck St. Hedwig Kliniken Berlin GmbH Klinik für Anästhesie und Intensivmedizin Große Hamburger Straße 5-11 10115 Berlin

	Investigators: Moritz Schmidt 4) Minden **<u>Principal investigator:</u>** Prof. Dr. med. Bernd Bachmann-Mennenga Head of Department of Anesthesiology Johannes Wesling Klinikum Minden Department of Anesthesiology Mühlenkreiskliniken (AöR) Hans-Nolte-Straße 1 32429 Minden Germany Tel: +49 571 790 – 4401, Fax: +49 571 790 – 294400 E-Mail bbm@muehlenkreiskliniken.de **Authorized Representative investigator** OA Dr. med. Mario Kluth Johannes Wesling Klinikum Minden Department of Anesthesiology Mühlenkreiskliniken (AöR) Hans-Nolte-Straße 1 32429 Minden Germany Investigators: Katrin Siggelkow Helmut Warkantin Cornelia Buhrke Dr. Gerhard Adam Prippenow 5) Homburg (no recruitment after initiation) **<u>Principal investigator</u>** Prof. Dr. med. Thomas Volk Universitätsklinikum des Saarlandes Department of Anesthesiology and Intensive Care Medicine and Pain Management Gebäude 57 66421 Homburg Germany Tel.: +49 6841/16-22485 Fax: +49 6841/16-22589 E-Mail: nicole.schmidt@uniklinikum-saarland.de Investigators: Alexander Wolf Dr. med. Michael Glas
7) study centers	<u>Multicenter, 4 active centers:</u> 1)

	Department of Anesthesiology and Intensive Care Medicine Campus Charité Mitte and Campus Virchow - Klinikum Charité - University Medicine Berlin Augustenburger Platz 1 13353 Berlin Germany 2) Lichtenberg Sana Klinikum Lichtenberg, Oskar-Ziethen-Krankenhaus Department of Anesthesiology Fanningerstraße 32, 10365 Berlin 3) St. Hedwig St. Hedwig Kliniken Berlin GmbH Department of Anesthesiology and Intensive Care Medicine Große Hamburger Straße 5-11 10115 Berlin 4) Minden Johannes Wesling Klinikum Minden Department of Anesthesiology Mühlenkreiskliniken (AöR) Hans-Nolte-Straße 1 32429 Minden 5) Homburg (no recruitment after initiation) Universitätsklinikum des Saarlandes Department of Anesthesiology and Intensive Care Medicine and Pain Management Gebäude 57 66421 Homburg
8) Publication of the trial (Reference)	Publication is planned in a peer reviewed journal. Planned publication title: *Etoricoxib reduces postoperative pain in Colon or Rectal fast-track surgery both at rest and on movement.* Clincialtrials.gov: NCT01259830
9) Study period	First patient, first visit: 07.03.2011 Last patient, last visit: 14.03.2014 <u>Recruitment stop : 29.03.2014</u> At the 29.03.2014 the recruitment of he the trial was terminated (81 patients were already randomized and included), because of financial reasons. <u>Study stop: 28.04.2014</u> Because of logistic and financial reasons the trial was terminated at the 28.04.2014. <u>Result of analysis:</u>

	Neither a higher serious adverse event (SAE) rate nor a higher adverse event (AE) rate was clearly recognizable in the Arcoxia® arm based on statistical evidence. No Adverse Drug Reactions (ADR) or Suspected Unexspected Serious Adverse Drug Reactions (SUSAR) were reported. The risk-benefit ratio of Arcoxia® in this clinical trial is favourable.
10) Phase of development	Therapeutic use (Phase IV)
11) Objectives	Primary endpoint: The average pain level (scale 0-10) in the area of surgery during movement (walking a fixed number of steps) under active epidural analgesia, at the third day following laparoscopic colon or rectal surgery. To demonstrate that the administration of etoricoxib 120mg additionally to the clinical routine therapy (epidural catheter) reduces the post-operative pain level during movement at the third day after laparoscopic colon or rectal surgery in the fast-track design. Secondary endpoints: 1. Post-operative pain level during movement in the first 2 days after laparoscopic colon or rectal surgery. [Time Frame: In the first 2 days after laparoscopic colon or rectal surgery] 2. Post-operative pain level during rest in the first 2 days after laparoscopic colon or rectal surgery. [Time Frame: In the first 2 days after laparoscopic colon or rectal surgery] 3. Post-operative pain level during rest and movement from the third (one day after epidural catheter removal) until the fifth day after laparoscopic colon or rectal surgery [Time Frame: In the first three days after epidural catheter removal] 4. Incidence of pain events and the average pain intensity in body parts outside of the area of operations. [Time Frame: In the first three days after epidural catheter removal] 5. Incidence of new organ dysfunctions (cardiovascular, gastrointestinal, renal, respiratory, cognitive, infective) [Time Frame: In the first nine days after laparoscopic colon or rectal surgery] 6. Postoperative LOS [Time Frame: Period of hospital stay, an exspected average of seven days] 7. Postoperative intensive care unit stay [Time Frame: Period of intensive care unit stay, an exspected average of one day]

	8. Amount and frequency of intake of rescue medication [Time Frame: In the first five days after laparoscopic colon or rectal surgery] 9. Incidence of side effects by IMP [Time Frame: In the first nine days after laparoscopic colon or rectal surgery] 10. Patients level of satisfaction [Time Frame: In the first five days after laparoscopic colon or rectal surgery]
12) Methodology	Study design: Prospective, doubleblind, randomised, placebo-controlled multicenter clinical trial phase IV. Screening period: Patients were screened during their visit in the preoperative anesthesia clinic regarding inclusion criteria. Baseline period: Baseline assessment including preoperative pain level and further investigations regarding the planned operation were performed after the informed consent in the preoperative anesthesia clinic. Treatment /placebo assignment was performed due to randomization. A unique identifier was assigned to each patient included. Treatments to be compared: Etoricoxib 120 mg/Placebo was administered in the morning of the operation day and in the following 5 postoperative mornings in three phases: Phase I: day 0 (operation day) and first postop day until morning of postop day 2, epidural catheter in place. Phase II: postop day 2, day of epidural catheter removal, change to paracetamol ((4 x 1 g/d) Phase III: postop days 3-5, analgesia with paracetamol (4 x 1 g/d) and morphine-i.v.-PCA. Rescue medication: Phase I: patient-controlled epidural analgesia Phase II and III: morphine-i.v.-PCA (3 mg Morphinboli all 5 minutes, if „pain on rest“ - NRS 3/10 or greater and pain on walking”-NRS 5/10 or greater) Procedures until postoperative day 9: During all visits and at the last visit (postoperative day 9), patients rate overall satisfaction with analgesic therapy on a 11-point numeric rating scale, pain levels, analgetica requirements, adverse events (side effects) length of hospital stay, length of intensive care unit stay and organ dysfunctions were reported.

Data were blinded until the analysis had been completed, protocol violations were documented.

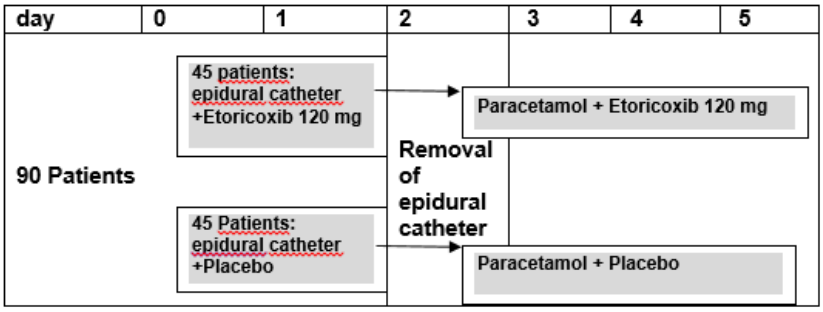

Figure 1: Treatment (per protocol)

Number of patients (planned and analysed)

Planned number of patients was 90 (45 patients in each group: Etoricoxib (Arcoxia®), placebo group (P-Tabletten weiß 8 mm Lichtenstein®). 81 were recruited, 68 were analysed.

Planned number of patients:

Sample size calculation

Sample size calculation is based on data from the acute pain service at Charité - Universty Medicine Berlin, which show a mean “pain on walking”-NRS of 5/10 at the third postoperative day with a standard deviation of 3 points.

Even assuming the standard deviation is similar (and not smaller) with treatment, a relevant reduction of 2 points on the NRS from 5/10 to 3/10 - a mean “pain on walking”-NRS of 3/10 is proposed.

This values are the basis for the following sample size calculation with nQuery Advisor® Release 7.0, Stat. Solutions Ltd. & South Bank, Crosse’s Green, Cork, Ireland:

Estimate of $p_1 = P(X<Y)$ from means and SD assuming normality

Group 1 mean, μ_1	5.0
Group 2 mean, μ_2	3.0
Difference in means, $\mu_1 - \mu_2$	2.0
Common standard deviation, σ	3.0
Effect size, $\delta = (\mu_1 - \mu_2) / \sigma$	0.667
$p_1 = P(X<Y)$	0.319

Wilcoxon (Mann-Whitney) rank-sum test that $P(X<Y) = .5$ (continuous outcome)

Test significance level, α	0.050
1 or 2 sided test?	2
$p_1 = P(X<Y)$	0.319
Power (%)	80
n per group	40

	Sample size is therefore calculated on the basis of a medium effect size (0.5), 80% power and an alpha error probability of 0.05, yielding a group size of 40 patients. Including a drop-out rate of 10%, a total of 90 patients (45 per group) needed to be included in the study. Analysed number of patients: 536 Patients were screened and 81 were randomized and included. Drop-out: 13 Patients were declared as drop-outs: In 6 drop-out-Patients exclusion criteria occurred, 7 drop-out-patients refused participation after study inclusion (see attachment figure 1 Consort-Flow-Diagram). Per- protocol analysis: This analysis was restricted to the participants who fulfil the protocol in the terms of the eligibility, interventions, and outcome assessment: From 68 patients 47 patients could be analysed per protocol. Intention to treat analysis In the following 21 patients protocol deviations occurred (analysis intention to treat): 13 protocol violations in the Verum group: • Deviation from planned analgesia scheme EBMK004 • First administration of study drug after the operation EBMK007 • Randomized from the wrong stratum, Deviation of analgesia via Epiduralcatheter EBMK009 • Randomized from the wrong stratum EBVK004 • Additive administration of NSAID (non-steroidal anti-inflammatory drugs) 6 ELK005 • Deviation of analgesia via an epidura lcatheter EMK005 • Deviation of analgesia via an epidural catheter EMR001 • Randomized from the wrong stratum ESK005 • Deviation of analgesia via an epidural catheter ESK007 • Chronic pain patient EBM002 • Chronic pain patient ELK008 • Deviation of analgesia via an epidural catheter EB006 • Deviation from planned analgesia scheme EBMK005 8 protocol violations in the Placebo group: • Randomized from the wrong stratum EBVK005 • Deviation of analgesia via an epidural catheter EL001 • Deviation of analgesia via an epidural catheter EMK003 • Randomized from the wrong stratum ESK003 • Randomized from the wrong stratum, Deviation from analgesia scheme ESR001

	• Deviation from planned analgesia scheme EBMR001 • Additive administration of NSAID (non-steroidal anti-inflammatory drugs) ELK017 • Deviation from planned analgesia scheme EBMK001 68 patients were analysed according to intention to treat.
14) Diagnosis and main criteria for inclusion	• aged 18 or over • written informed consent • no inclusion in other medical studies according to the AMG (German drug law) during the study period • realization of colon or rectal surgery in the fast track design after clinical standards including an epidural catheter • no allergy against etoricoxib, other components or other NSAID • no coronary heart disease • no heart insufficiency NYHA II-IV • no cerebrovascular disease • no peripheral arterial occlusive disease • no untreated arterial hypertonus • no ASA status IV-V • correct epidural catheter placement within 48 h after surgery
15) Test product, dose and mode of administration, batch number	Arcoxia® - Maximum dose is 120 mg/d oral administration for 6 days; Manufacturer: MSD SHARP & DOHME GMBH, Lindenplatz 1, 85540 Haar Batch numbers: 0463430, 1003010
16) Duration of treatment	The maximum duration of the study protocol (administration of Arcoxia) is in the morning (7 h) of the operation up to the morning of the 5th postoperative day. The study patients were followed up for 9 postoperative days in the hospital or at home by telephone visit (< 9 days in hospital).
17) Reference therapy, dose and mode of administration, batch number	P-Tabletten weiß 8 mm Lichtenstein®: Maximum dose is one tablet/d oral administration for 6 days; Manufacturer: Winthrop Arzneimittel GmbH Batch numbers: 3530315J, 3530318J, 3530317J
18) Criteria for evaluation: Efficacy and Safety	**Evaluation of Efficacy** **See attachment table 1** **Primary efficacy variable:** The average pain level (scale 0-10) in the area of surgery during movement (walking a fixed number of steps) under active

	epidural analgesia, at the third day following laparoscopic colon or rectal surgery. To demonstrate that the administration of etoricoxib 120mg additionally to the clinical routine therapy (epidural catheter) reduces the post-operative pain level during movement at the third day after laparoscopic colon or rectal surgery in the fast-track design. **Secondary efficacy variables:** 1. Post-operative pain level during movement in the first 2 days after laparoscopic colon or rectal surgery 2. Post-operative pain level during rest in the first 2 days after laparoscopic colon or rectal surgery 3.Post-operative pain level during rest and movement from the third (one day after epidural catheter removal) until the fifth day after laparoscopic colon or rectal surgery 4.Incidence of pain events and the average pain intensity in body parts outside of the area of operations 5. Incidence of new organ dysfunctions (cardiovascular, gastrointestinal, renal, respiratory, cognitive, infective) 6. Postoperative length of stay 7. Postoperative intensive care unit stay 8. Amount and frequency of intake of rescue medication 9. Incidence of side effects by IMP 10. Patients level of satisfaction **<u>Evaluation of Safety</u>** Adverse events
19) Statistical methods	For all targets, the findings are first analyzed exploratory and descriptively, i.e. statistical measures such as mean and variance (metric traits), median and interquartile range (ordinal characteristics) and reached frequencies with percentages at nominal characteristics determined. A review of the distributions of continuous features for normality supplements this analysis (not shown separately). Since the primary endpoint will be determined as an average of scores (categorical), a confirmatory method of analysis of the nonparametric Mann-Whitney U-test for independent groups is considered. Secondary endpoints are analyzed depending on scaling of the observation values with the Mann-Whitney U test or the exact/asymptotic $\chi 2$ test for independent samples to be significantly different. In the case of small and / or imbalanced sample sizes, strong (and many) relationships in the data or only sparsely occupied contingency table exact variants of these tests are applied.

	The indicated analysis each may be supplemented with covariance and said as stratification factors as a covariate, in addition, a separate analysis for individual strata (such as center, surgery) was carried out with a comparison of the results. Even though the pain intensities are average measurements for practical reason (several times a day raised) used in the clinic, they are statistically repeated (dependent) observations, which should be adequately evaluated statistically. A general statement about any differences in the treatment arms is therefore definitively to meet only when both the entire time course of the observed toxicities using a non-parametric analysis of variance for repeated measures and the differences in particularly important moments (univariate post hoc tests) analyzed. The test level is defined in all cases to α = 5% (two-sided) set, carried out over the two-group comparison of the primary endpoint also comparisons to be understood in the sense of an exploratory analysis, i.e. an adjustment of the alpha error is not performed. The analysis of the study results is carried out by the "intent-to-treat" - principle.
20) Summary Conclusion **Efficacy Results** **Safety Results** **Conclusion**	**ANALYZED DATA** Following the data collection was carried out the investigators performed a detailed plausibility check of the data. Only after approval by the clinical monitor the data has been transferred to the database. Within the database, also a plausibility check under the 4-eye-principle by two investigators took place. After completion of the database, the randomization group was unblended and the whole database was transferred to the statistician Prof. Dr. Klaus-Dieter Wernecke. Of the 68 patients, 47 patients were treated and evaluated in accordance with the study protocol. In the remaining 21 patients were protocol violations before, so they were evaluated “intention-to-treat”. Serious protocol violations, which lead to the ITT analysis include: 1. stratification in the wrong treatment arm 2. variation in the length of treatment with the epidural catheter 3. delivery of systemically active pain drugs apart from paracetamol and opioids from the 3.POD 4. administration of NSAID 5. Chronic pain patients 6. First administration of the IMP after surgery In the occurence of protocol violations there is no significant difference related to both treatment arms (Fisher’s exact test). **Demographic Data and Baseline Characteristics:** The intent-to-treat population includes 36 patients in the etoricoxib group and 32 patients in the placebo group. The gender distribution is balanced (p = 0.614). The median age in the etoricoxib group is 51 years and 61 years in the placebo group, so that the patients in the etoricoxib group are significantly younger than in the placebo group (p = 004).

EFFICIACY RESULTS:
See attachment table 1

Primary efficacy endpoint:
Chronological Sequence of Pain Intensity on Movement in the Area of the Surgical Intervention (Figure 2) was the primary efficacy variable.

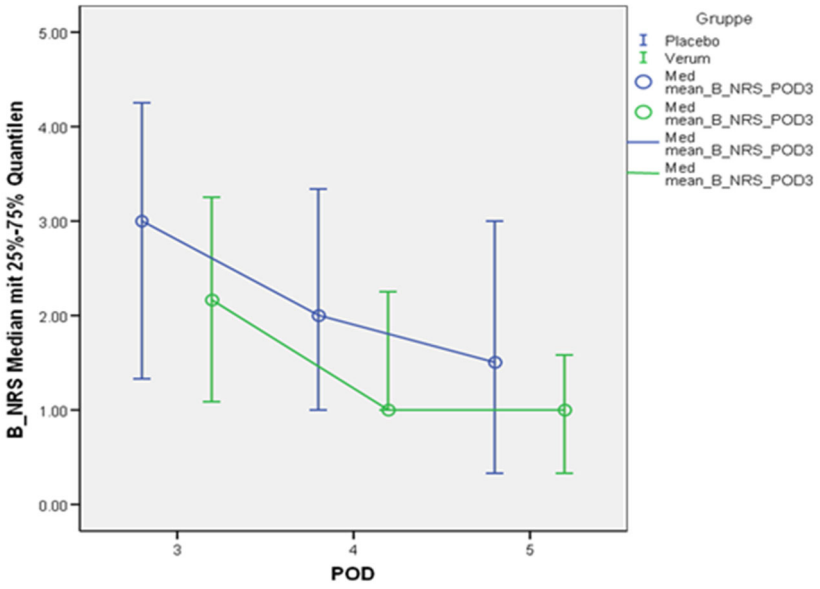

Figure 2: Chronological Sequence of Pain Intensity on movement in the area of the surgical intervention

For the **primary endpoint** of the shows at the small number of cases, the trend that the administration of etoricoxib reduces the pain, but it is not significantly detectable (p = 0.109).

Secondary endpoints:
For the secondary efficacy endpoints, there was, except in mean NRS measured at rest (p = 0.034 at 3.POD, p = 0.025 on 4.POD and p = 0.041 on 5.POD) no difference between the p-values.

1. Post-operative pain level during movement in the first 2 days after laparoscopic colon or rectal surgery.

While the analgesia is carried out successfully over the epidural catheter (first and second day after the operation), the additional administration of etoricoxib has no positive effect on pain intensity on movement (p = 0.814).

2. Post-operative pain level during rest in the first 2 days after laparoscopic colon or rectal surgery.

Measurement is the mean of three measurements of pain intensity at rest in the surgical area on each study day. On the first two postoperative days, the pain scores were analyzed at times, as long as the epidural catheter was successfully working. On average, the NRS values of the study patients were at rest at the surgical site with the median below the intervention limit of NRS = 4. The highest median reached the post-operative pain on the 3rd day after surgery after removal of the epidural

	catheter. After the epidural catheter has been removed, the additional administration of etoricoxib decreases the mean NRS measured at rest (p = 0.034 at 3.POD, p = 0.025 on 4.POD and p = 0.041 on 5.POD). **3. Post-operative pain level during rest and movement from the third (one day after epidural catheter removal) until the fifth day after laparoscopic colon or rectal surgery** This trend that the administration of etoricoxib reduces the pain can also be seen on the 4th (p=0.103) and 5th (p=0.087) day after surgery. **4. Incidence of pain events and the average pain intensity in body parts outside of the area of operations.** Chronological sequence of pain intensity in areas outside the area of surgery: Measurement is the mean of three measurements of pain intensity outside the surgical area on each study day. Overall, the incidence of pain outside the surgical area was very low. The mean of pain outside the area of surgery was at all subsequent time points below a NRS of 1. Because the pain occurrence outside the surgical area was very low overall, no analgesic effect was found through the additive administration of etoricoxib. **5. Incidence of new organ dysfunctions (cardiovascular, gastrointestinal, renal, respiratory, cognitive, infective)** Overall, the patients developed 179 organ dysfunctions. For none of patients with complications a significant difference between the groups (verum vs. placebo) has been shown (p = 0.380) (Table 1). In the vast majority is light organ complications. As the characteristic side effects of coxibs also the number of occurrences of hypertensive episodes was studied in both groups. Hypertensive crisis after gastrointestinal operations could occur in the context of pain, anxiety and stress, or even in poorer absorption of oral antihypertensive drugs. A total of 12 (Placebo: 6 /Verum: 6) hypertensive episodes have been reported in the ITT population, which is equally distributed on the etoricoxib as well as in the placebo group (p = 0.822, asymptotic $\chi 2$ test). **6. Postoperative LOS** No difference in regard of hospital stay between treatment groups. (p=0.691). **7. Postoperative intensive care unit stay** No difference in regard of intensive care unit stay between treatment groups. (p=0.220). **8. Amount and frequency of intake of rescue medication** Comparison of the requirement of opioids with and without etoricoxib: Retrieval of rescue medication via patient-controlled-

	analgesia and the additive administered opioids for postoperative pain management defined the opioid requirement. The total requirement of opioids decreases over the duration of study participation. The administration of etoricoxib does not show any opioid-saving effects at any of the postoperative days (p = 0.879 at 3.POD, p = 0.682 on 4 POD and 0.871 on 5.POD). **9. Incidence of side effects by IMP** 1 Adverse event was evaluated as related to the study drugs. The adverse drug reaction "Urticaria" occurred in the female study patient ELK008 1 hour after the sixth administration of the study drug (Arcoxia® 120mg/d). **10. Patient Satisfaction** Patient satisfaction increases over the duration of study participation with decreasing pain intensity and decreasing opioid requirements. A difference in the two treatment arms could not be demonstrated (p = 0.849). **Evaluation of Safety** The safety analysis is based on 81 study patients (Arcoxia® (n=40), P-Tabletten weiß 8 mm Lichtenstein® (n=41)). A detailed Safety analysis was sent to the authority (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM)) and the ethical commission (LaGeSo) in June 2015. During this study no Suspected Unexspected Serious Drug Reactions were observed. One Adverse Drug reaction was observed in the Verum group "Urticaria". No early unblinding was necessary during the trial. The use of study medications (Arcoxia®/P Lichtenstein 8 mm weiß®) has to be considered as safe. The risk-benefit ratio did not change during this trial. Adverse events (AEs): 49 AEs in 34 study patients were documented in this study. 9 AEs occurred in 6 drop-outs: EBV001, EBMK003, EBMK008, EBVK003, EBVR007, ESK004. In 17 study patients of the Verum group 26 AEs occurred; in 17 study patients in the Placebo group 23 AEs occurred. This difference is not significant. The intensity of the adverse events was mild (53.1%) und moderate (34.7%) and severe (12.2%). 48 adverse events were not considered as related to the study drugs and no unblinding was necessary. 1 AE was evaluated as related to the study drug, which showed after unblinding that it was no adverse drug reaction: Adverse event "rotary vertigo" in female patient EBVK003 occurred 1 hour after first administration of study drug (Placebo).

	1 AE was evaluated as related to the study drugs, which showed after unblinding that it was an adverse drug reaction: The adverse drug reaction “Urticaria” occurred in the female study patient ELK008 1 hour after the sixth administration of the study drug (Arcoxia® 120mg/d). <u>Serious adverse events (SAEs):</u> 9 SAEs in 8 study patients occurred in this study, 6 SAEs occurred in the Verum group, 3 SAEs occurred in the Placebo group. In the study patient EBVR007, who was declared as drop-out patient (reason: lack of compliance) altogether 2 SAEs (SAE No. 1 High spinal block, SAE No. 2 Sensible block) were reported. No unblinding was necessary. The study patient showed no sensomotoric failures in the clinical course; all impairments were reversible. In study patient ELK016, which was declared a drop - out (reason: no epidural catheter placement possible) 1 SAE (SAE No. 1 Bradycardia during attempt of epidural catheter placement) was reported. No unblinding was necessary. The intensity of the SAEs was mainly severe 4 SAEs (44.4%) or moderate 4 SAEs (44.4%) and 1 SAE was mild (11.2%). All serious adverse events were not considered as related to the study drugs and no prior unblinding was necessary. <u>Death of study patients:</u> No death Due to protocol violations 13 study patients were declared as drop-outs prior to unblinding, 4 in Verum group, 9 in the Placebo group **<u>CONCLUSION:</u>** The main findings of the study are that additive administration of etoricoxib decreases pain intensity in the surgical area on each postoperative day after the pain therapy via the epidural catheter is finished. These results apply during rest as well as on movement. By the administration of etoricoxib there is no opioid sparing effect. The use of study medications (Arcoxia®/P Lichtenstein 8 mm weiß®) has to be considered as safe.
Date of report: 27.07.2015 amended on 16.04.2019	

Attachment:

Figure 1: Consort-Flow-Diagram

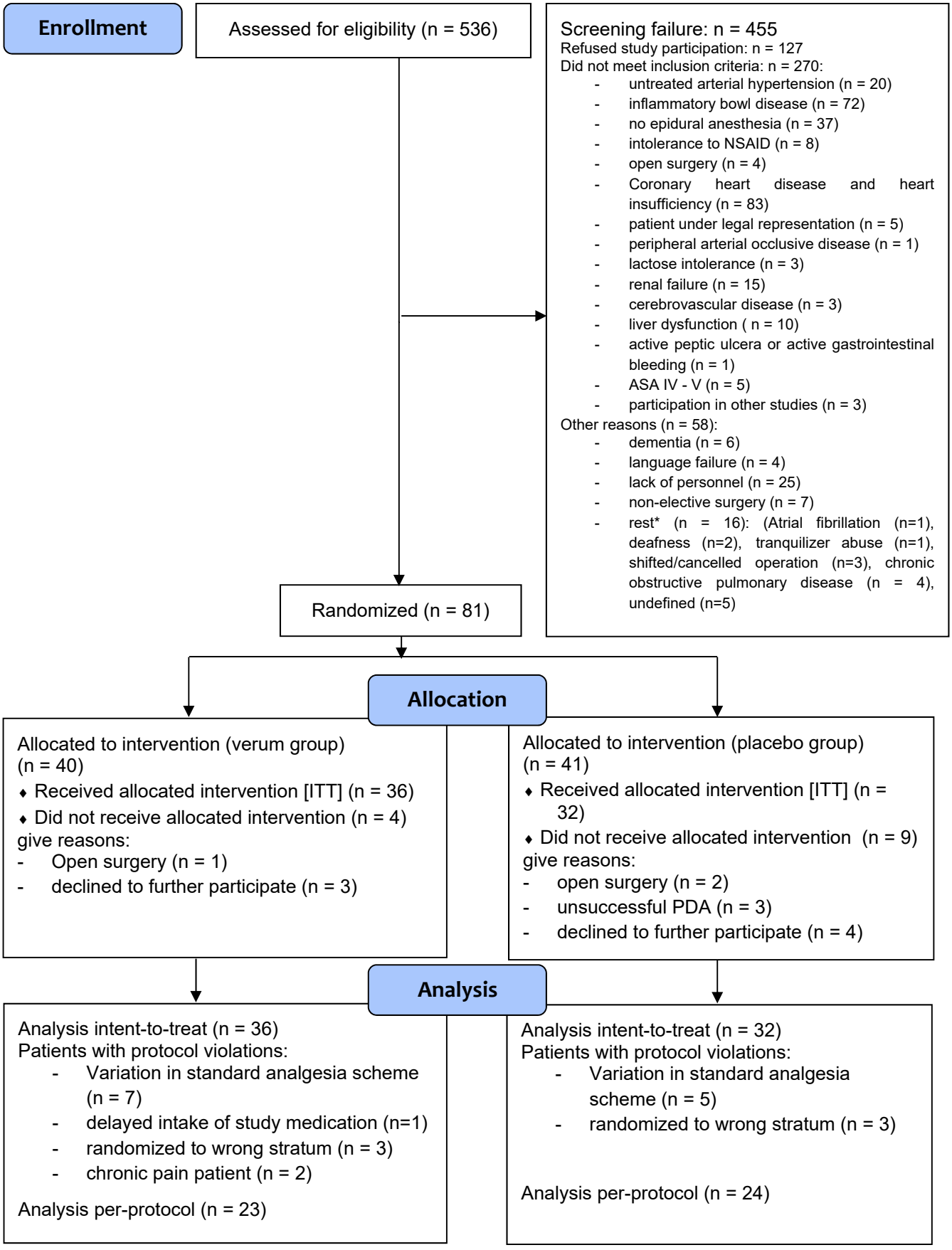

Table 1: Study efficacy variables

	Etoricoxib n=36	Placebo n=32	p
Primary endpoint: NRS on POD3 (movement) median; IQR	2.1667 [1.0833;3.25]	3 [1.3333;4.25]	0.109[a]
Secondary endpoints:			
NRS on POD1+2 (movement) median; IQR	1.875 [1.0417;3]	2.0417 [1.375;3.0625]	0.814[a]
NRS on POD4 (movement) median; IQR	1 [1;2.25]	2 [1;3.3333]	0.103[a]
NRS on POD5 (movement) median; IQR	1 [0.3333;1.5833]	1.5 [0.3333;3]	0.087[a]
NRS on POD1+2 (rest) median; IQR	0.5000 [0;1.4583]	0.9167 [0;1.6250]	0.913[a]
NRS on POD3 (rest) median; IQR	1.0 [0;1.3333]	1.8333[0.833;3]	**0.034[a]**
NRS on POD4 (rest) median; IQR	0.3333 [0;1]	1.3333 [0;2.3333]	**0.025[a]**
NRS on POD5 (rest) median; IQR	0 [0;0.9167]	0 [0;0.9167]	**0.041[a]**
NRS outside operation area median; IQR **POD1+2** **POD3** **POD4** **POD5**	 0.2083 [0;1.833] 0 [0;1.1667] 0 [0;1] 0 [0;0.9167]	 0.2197[0;1.2197] 0 [0;1] 0 [0;1] 0 [0;0]	 0.962[a] 0.504[a] 0.919[a] 0.319[a]
Sum organ dysfunctions median; IQR	2 [1;3]	3 [1;5]	0.380[a]
Postoperative length of stay [d] median; IQR	11 [8;25]	10 [8.25;10]	0.691[a]
ICU-LOS [hours] median; IQR	48[23.5;169]	32 [19.25;48]	0.220[a]
Intake of rescue medication median; IQR **POD3** **POD4** **POD5**	 9 [0;25.8325] 6.665 [0;20.25] 0 [0;8.25]	 10.5 [0;30] 3 [0;14.5] 0 [0;8.4175]	 0.879[a] 0.682[a] 0.871[a]
Patient satisfaction; total median; IQR	10 [9;10]	10 [8;10]	0.849[a]

Legend:
a Mann Whitney exact