2 SYNOPSIS

Name of Sponsor/company: Develco Pharma Schweiz AG	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
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Title of the study:

Randomised, double-blind, cross-over Phase III study to investigate the efficacy and safety of hydromorphone after once daily administration of Hydromorphone HCl PR tablets XL in comparison to twice daily administration of Palladon® retard capsules in patients with chronic severe cancer or non-cancer pain.

Investigators:

Coordinating investigator: Professor Dr. med. Michael Schäfer, Klinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin der Charité –- Universitätsmedizin Berlin, Campus Charité Mitte und Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany

Study centres:

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Four active sites in Poland: Dr Agata Chemperek-Wroczek (21), Dr Aleksandra Cialkowska-Rysz (site 22), Dr Magdalena Korozan (site 24), Dr Mariola Lembas-Sznabel (site 25)

Publication:

Not applicable

Study period:	**Phase of development:**
12 April 2012 (first patient screened) 31 July 2012 (last patient completed)	III

Objectives:

Primary objective:

To demonstrate that once daily administration of Hydromorphone HCl PR tablets XL is not inferior compared to a twice daily administration of Palladon® retard capsules at the same daily dosage.

Secondary objectives:

- In case of non-inferiority, to demonstrate that once daily administration of Hydromorphone HCl PR tablets XL is more effective (superior) as twice daily administration of Palladon® retard capsules at the same daily dosage.
- To assess the safety and tolerability of once daily administration of Hydromorphone HCl PR tablets XL in comparison with twice daily administration of Palladon® retard capsules.

Methodology:

This was a prospective, multicentre, randomised, double-blind, active-controlled, adaptive, two-treatment, two-period, two-sequence, crossover study with 8-days active washout in patients with chronic severe cancer or non-cancer pain.

After screening, eligible patients entered a titration / stabilisation period during which their hydromorphone HCl medication was titrated to provide adequate and stable pain relief. Patients who did not take hydromorphone HCl at screening were switched to hydromorphone HCl at the start of the titration / stabilisation period. After the patients were on a stable dose of hydromorphone HCl for at least 3 consecutive days they were randomised to double-blind treatment to start with either the test or the reference study medication.

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Patients were treated for 13 days in each period. At the end of the first period patients immediately crossed over to the second period.

During the titration / stabilisation period and the two 13-day double-blind treatment periods the patients recorded their pain intensity (PI) daily in a patient diary.

A follow-up examination was performed 9 - 14 days after the end of the second treatment period (between Day 35 and Day 40).

Number of subjects:

Planned: 76 randomised patients in total

Randomised: 40 in total

Safety Analysis (SA) Set: 37 in total

Full Analysis Set (FAS): 36 in total;
18 in sequence I (test – reference) and18 in sequence II (reference – test)

Per Protocol Set (PPS): 31 in total;
16 in sequence I (test – reference) and 15 in sequence II (reference – test)

Inclusion criteria:

1. Male and female patients ≥18 years of age.
2. Patients with chronic severe cancer or non-cancer pain.
3. Patients with predominantly non-neuropathic pain (assessed by the DN4 Neuropathic Pain Diagnostic Questionnaire).
4. Patients with documented history of chronic severe pain that required around-the-clock opioid therapy and were likely to benefit from WHO step III opioid therapy for the duration of the study.
5. Women of childbearing potential agreeing to undergo pregnancy tests.
6. Patients willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending scheduled visits, completing telephone contacts, and compliance with protocol requirements as evidenced by providing signed written informed consent.
7. For inclusion in double-blind treatment phase adequate analgesia (mean "current" pain intensity per day >0 mm and ≤40 mm on Visual Analogue Scale [VAS]) prior to randomisation for at least three consecutive days.
8. For inclusion in double-blind treatment phase stable analgesic requirements of at least 8 mg hydromorphone HCl per day prior to randomisation for at least three consecutive days (stable maintenance dose of hydromorphone; ≤2 doses of rescue medication per day), tolerable adverse events (AEs).

Exclusion criteria:

1. Patients with any situation in which opioids are contra-indicated, severe respiratory depression with hypoxia and/or hypercapnia, severe chronic obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, paralytic ileus.
2. Hypersensitivity to hydromorphone or any of the excipients of the study medication.
3. Patients requiring less than 8 mg or more than 32 mg hydromorphone HCl per day at the start of the double-blind treatment phase.
4. Surgery within 1 month prior to study start or anticipated or scheduled surgical intervention during the study.
5. Intravenous chemotherapy or radiotherapy for pain alleviation or neural blockade within 2

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weeks prior to study start or anticipated or scheduled during the course of the study.

6. Known or suspected significant hepatic impairment (hepatic transaminases >3 times the upper limit of normal).
7. Known or suspected severe renal impairment (creatinine clearance [CRCL] <30 ml/min) or patients with renal failure who are on any form of dialysis.
8. Known or suspected significant circulatory disturbance, hypotension, or circulatory shock.
9. Known or suspected clinically relevant endocrine disorder, such as myxoedema, not adequately treated hypothyroidism or adrenocortical insufficiency (e.g. Addison's disease).
10. Known or suspected clinically significant bowel disease (e.g. paralytic ileus, significant impairment of bowel motility severe enough to potentially result in ileus, obstructive or inflammatory bowel disease).
11. Known or suspected acute or chronic pancreatitis or biliary tract disease.
12. Any gastro-intestinal pathology or surgery or intractable vomiting likely to significantly influence drug absorption.
13. Inability to swallow the study drugs whole (e.g. due to dysphagia).
14. Known or suspected significant prostatic hypertrophy or urethral stricture severe enough to potentially result in urinary retention.
15. Known or suspected CNS depression (signs/symptoms: decreased vital signs, impaired thinking and perception, slurred speech, slowed reflexes, fatigue, decreased consciousness), coma, or convulsive disorder.
16. Known or suspected elevation of intracranial pressure.
17. Known or suspected acute alcoholism, delirium tremens, or toxic psychosis.
18. History of drug addiction or drug seeking behaviour.
19. Concomitant treatment with monoamine oxidase (MAO) inhibitors.
20. Pregnancy or breast-feeding. Women of childbearing potential unable or unwilling to practice adequate contraceptive measures. Reliable methods for women were hormonal contraceptives, surgical intervention (e.g. tubal ligation), intrauterine device (IUD) and sexual abstinence.
21. Any other condition of the patient that in the opinion of the investigator may have compromised evaluation of the study treatment or may have jeopardized patient's safety (e.g. risk of suicide), compliance or adherence to protocol requirements.
22. Previous enrolment in this study or participation in any other drug investigational trial within the past 30 days (or five half-lives whichever is longer) prior to enrolment.
23. Persons committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

Test product, dose and mode of administration, batch number:

Hydromorphone HCl 8 mg / 16 mg / 32 mg PR tablets XL

The Total Daily Dose (TDD) was determined individually for each patient. Oral administration once-daily (morning dose only).

Batch numbers:

- Hydromorphone HCl 8 mg PR tablets XL, batch no.: 14201
- Hydromorphone HCl 16 mg PR tablets XL, batch no.: 10101
- Hydromorphone HCl 32 mg PR tablets XL, batch no.: 02502

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Reference product, dose and mode of administration, batch number:

Palladon® retard 4 mg / 8 mg / 16 mg capsules

The TDD was determined individually for each patient. Oral administration twice-daily (morning and evening dose).

Batch numbers:

- Palladon® retard 4 mg capsules, batch no.: 10068389
- Palladon® retard 8 mg capsules, batch no.: 10068237
- Palladon® retard 16 mg capsules, batch no.: 10068787

Titration / Stabilisation period (maximum 14 days):

- Palladon® retard 4 mg / 8 mg / 16 mg capsules were administered (swallowed as a whole) at 12-hour intervals. The TDD of this medication was determined individually for each patient by the investigator.
- Rescue medication: Palladon® capsules 1.3 mg (immediate release hydromorphone HCl), were taken as needed in intervals of at least 4 hours, in case of pain exacerbation or breakthrough pain.

Treatment was started with 8 mg hydromorphone HCl per day (e.g. in opioid-naïve patients) or at higher daily doses depending on the patient's previous opioid therapy. Dosage adjustment was performed every 2 days if required based on the assessments of pain intensity and the amount of rescue medication taken. A single dose of rescue medication was equivalent to 10% of the current TDD of hydromorphone HCl (e.g. 3.9 mg immediate release hydromorphone HCl for a TDD of 32 mg prolonged release hydromorphone HCl) and could be taken every 4-6 hours.

The TDD was adjusted as needed in steps of 8 mg to realise one of the following stages of the TDD, namely 8 mg, 16 mg, 24 mg or 32 mg prolonged release hydromorphone HCl per day. When adequate and stable analgesia was attained – defined as mean "current" pain intensity (i.e. the "current" PIs at the four scheduled time points and the "current" PIs before administration of rescue medication) per day >0 mm and ≤40 mm on a VAS, a stable maintenance dose of hydromorphone (≥8 mg to ≤32 mg hydromorphone HCl per day), and not more than 2 doses of rescue medication per day for the last three consecutive days – the patients were randomised to double-blind treatment with the investigational medicinal products.

Double blind treatment periods:

Two 13-day double-blind treatment periods (Period 1: Day 1 to Day 13; Period 2: Day 14 to Day 26):

The individual TDD of hydromorphone HCl was calculated from the final TDD in the titration / stabilisation period. Dosage adjustment of the test and/or reference treatment was not allowed during the double-blind treatment periods.

- Test product (Hydromorphone HCl PR tablets XL): was taken once daily in the morning at approximately 08:00 h ± 30 minutes. For visits at Day 1 (randomisation), Day 14 (end of period 1) and Day 27 (end of period 2), the patient was not to take the morning dose before the visit at the study doctor. This visit was done between 08:00 h and 10:00 h in the morning. The same number of placebo units (neutral filler) were taken in the evening at approximately 20:00 h ± 30 minutes. Both test product and placebo (neutral filler) were blinded by encapsulation.
- Reference product (Palladon® retard capsules): was taken twice daily in the morning and in the evening at approximately 08:00 h ± 30 minutes and 20:00 h ± 30 minutes in two equally

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divided doses. For visits at Day 1 (randomisation), Day 14 (end of period 1) and Day 27 (end of period 2), the patient was not to take the morning dose before the visit at the study doctor. This visit was done between 08:00 h and 10:00 h in the morning. The reference product was blinded by encapsulation.

- Rescue medication: Palladon® capsules 1.3 mg (immediate release hydromorphone HCl) were supplied as rescue medication throughout the double-blind treatment periods.

A single dose of rescue medication was equivalent to 10% of the current TDD of hydromorphone HCl (e.g. 3.9 mg immediate release hydromorphone HCl for a TDD of 32 mg prolonged release hydromorphone HCl) and could be taken every 4-6 hours.

Duration of study:

During the titration / stabilisation period patients were titrated up to 14 days until adequate and stable pain control was achieved.

After stabilisation and randomisation, the patients underwent two 13-day treatment periods. An active washout phase of 8 days was included in each treatment period, during which the treatments (test and reference) were changed and new steady state conditions were reached.

A follow-up examination was performed 9 - 14 days after the end of the second treatment period (between Day 35 and Day 40).

Total duration of study: up to 54 days for each patient

Criteria for evaluation:

Efficacy:

Pain intensity (PI) score on 0 - 100 mm VAS

PI was assessed:

- at screening;
- during the open-label titration / stabilisation period and at the end of the open-label stabilisation period (baseline);
- during the two double-blind treatment periods.

PI was assessed four times daily (allowed deviation ±30 minutes) during the open-label titration / stabilisation period and during the two double-blind treatment periods at the following time points:

- 08:00 h (before drug intake),
- 12:00 h,
- 16:00 h,
- 20:00 h (before drug intake).

At these time points, patients rated their "current" PI.

In addition, patients rated their "current" PI:

- before administration of any rescue medication.

PI assessments at 08:00 h and 20:00 h also comprised ratings of PI over the past 12 hours ("recalled pain during day"- and "recalled pain during night"-time).

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For randomisation:

- mean "current" PI (i.e. the "current" PIs at the four scheduled time points and the "current" PIs before administration of rescue medication) per day >0 mm and ≤40 mm on VAS
- stable maintenance dose of hydromorphone (≥8 mg to ≤32 mg hydromorphone HCl per day)
- not more than 2 doses of rescue medication per day

was required for each of the last three consecutive days of the titration / stabilisation period.

In order to avoid carry-over effects, only the PI scores measured during the last 5 days of each 13-day double-blind treatment period were considered for efficacy analysis.

From the PI scores the following was calculated:

Primary efficacy endpoint:

- the mean "current" PI over all time points of the last 5 treatment days of period 1 and 2, i.e. the "current" PIs at the four scheduled time points and the "current" PIs before administration of rescue medication (= overall "current" PI).

Secondary efficacy endpoints:

- the mean "recalled pain during night" for the last 5 treatment days of period 1 and 2
- the mean "recalled pain during day" for the last 5 treatment days of period 1 and 2
- the mean "current" PI, i.e. the "current" PIs at the four scheduled time points and the "current" PIs before administration of rescue medication, for each of the last 5 treatment days of period 1 and 2 (= mean "current" PI per day, e.g. mean "current" PI score on Day 9)
- the mean "current" PI for each of the four scheduled time points over the last 5 treatment days of period 1 and 2 (= mean "current" PI per time point; e.g. mean "current" PI score at 08:00 h)

Rescue medication

Secondary efficacy endpoints:

The use of rescue medication was recorded throughout the titration period and the double-blind treatment periods. The following was determined:

- the daily dose of rescue medication for each of the last 5 treatment days of period 1 and 2 as documented in the daily diaries
- the mean daily dose of rescue medication for the last 5 treatment days of period 1 and 2 as documented in the daily diaries
- the total amount of rescue medication for the last 5 treatment days of period 1 and 2 as documented in the daily diaries
- the total amount of rescue medication during each treatment period as documented in the daily diaries
- the total amount of rescue medication during each treatment period as documented in the Case Report Form (CRF) (= supplied rescue medication minus returned medication in each treatment period)

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Overall effectiveness on 0 – 3 categorical scale (CAT)

Secondary efficacy endpoint:

Overall effectiveness (pain control over the previous 13 days of double-blind treatment) was assessed by patients and investigators at the end of each treatment period (in the morning on Day 14 and Day 27).

Safety / Tolerability:

Adverse events (AEs)

- Patient's self-assessment using daily diaries and investigator records at the end of each treatment period. AEs were assessed for seriousness, intensity and drug-event relationship.

Vital signs

- Blood pressure, pulse rate, body temperature, and respiration rate at screening, at the end of titration period, at the end of each treatment period and at the follow-up examination.

Laboratory

- Haematology, biochemistry, and urinalysis at screening and at the follow-up examination. In women of childbearing potential, a pregnancy test was performed at screening and at follow-up.

Statistical methods

A two-sided 95% confidence interval was used to test the hypothesis of non-inferiority of Hydromorphone HCl PR tablets XL dosed once daily to Palladon® retard capsules dosed twice daily (both providing an identical TDD for the patient).

Analyses of the efficacy variables were performed for the FAS and the PPS. The primary population subset was the PPS and not the FAS population as this preserves a conservative decision when using non-inferiority testing. All confirmatory testing was based on this subgroup. For further descriptive purposes, the same statistical procedures were applied to the FAS.

The study was powered to detect non-inferiority of the test product compared with the reference product in the primary efficacy endpoint, overall "current" PI on 0 - 100 mm VAS (mean "current" PI of the last 5 days of each treatment period).

Assessment of non-inferiority

The primary efficacy endpoint, overall "current" PI on 0 - 100 mm VAS (mean "current" PI of the last 5 days of each treatment period), was analysed by means of an analysis of covariance (ANCOVA), including the factors sequence, patient within sequence, period and treatment and the total amount of rescue medication during each treatment period as documented in the CRF (= supplied rescue medication minus returned medication in each treatment period) as additional co-variable. Only if the co-variable had a significant effect, the full ANCOVA was to be used; otherwise, the co-variable was to be dropped from the model. Non-inferiority of Hydromorphone HCl PR tablets XL for once daily dosing was to be concluded if the upper limit of the two-sided 95% confidence interval (CI) of the treatment difference between the test product and Palladon® retard capsules did not exceed 9 mm in the overall "current" PI on 0 - 100 mm VAS (mean "current" PI of the last 5 days of each treatment period). The two-sided 95% confidence interval for the treatment difference was computed based on the residual standard error of the corresponding factorial model.

Assessment of superiority

Only if the first primary hypothesis for non-inferiority was shown, then in a second step superiority of Hydromorphone HCl PR tablets XL for once daily dosing versus Palladon® retard capsules was to be

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based on the same two-sided 95% CI as above. If this interval did not exceed 0 mm, then superiority was to be concluded. Such *a priori*-order hypotheses allow testing both hypotheses on the same confidence/significance level.

Safety

All safety data obtained in this study are listed and tabulated with descriptive group statistics (mean, standard deviation, minimum, maximum, number of valid cases). Comparisons between treatment groups are based on descriptive statistics.

Sample size calculation

As a preliminary estimate, 76 patients in total (38 per treatment sequence) were planned to be randomised into the study. The sample size could be adjusted with an un-blinded interim analysis.

A difference of 9 mm in overall "current" PI was selected as the largest acceptable difference of the test treatment compared to the reference treatment.

The review of comparable studies with use of opioids in chronic cancer pain revealed a bandwidth for the standard deviation between patients of 10 - 24 mm. Conservatively, it was assumed that there would be no correlation between the two treatment periods, leading to conservative sample sizes compared to a higher correlation. For these reasons, a re-assessment of the between- and within-patient variation based on an un-blinded interim analysis was planned to address this uncertainty and re-calculate the sample size needed.

Adaptive, un-blinded interim analysis

After completion of 31 patients (per protocol), an adaptive, un-blinded interim analysis was performed in order to obtain reliable data for a re-estimation of the standard deviation and make further decisions for stopping the study due to early success or inefficacy or to continue the study with an adapted sample size. An adaptive interim analysis following the approach of Bauer and Köhne (Bauer P & Köhne K 1994) was chosen. This method is based on Fisher's combination test and controls the overall significance level of the test decision.

An IDMC performed the un-blinded interim analysis.

SUMMARY AND CONCLUSIONS

After 31 patients in the PPS had completed the study an Independent Data Monitoring Committee (IDMC) performed an un-blinded interim analysis.

The interim analysis demonstrated the non-inferiority of once daily Hydromorphone HCl PR tablets XL to twice daily Palladon® retard capsules. Other than the definition provided in the protocol and the SAP, the primary endpoint in this initial interim analysis was calculated as the mean of the "current" PIs at the four scheduled time points over the last five days only. Following the recommendation of the IDMC, the sponsor decided to terminate the study due to early success.

The conclusion of the IDMC of non-inferiority was confirmed for the primary efficacy endpoint of the study calculated as planned in the protocol and the SAP as the mean "current" PI over all time points of the last 5 treatment days of period 1 and 2, i.e. the "current" PIs at the four scheduled time points and the "current" PIs before administration of rescue medication (= overall "current" PI).

At early completion of the study, 37 patients (SA set) with a mean age of 57.9 years who required continuous opioid treatment for chronic cancer (N=3) or non-cancer (N=34) pain were treated with once daily Hydromorphone HCl PR tablets XL and twice daily Palladon® retard capsules.

EFFICACY RESULTS:

This study demonstrated that once daily Hydromorphone HCl PR tablets XL were non-inferior to twice daily Palladon® retard capsules in the primary efficacy endpoint. The difference in overall "current" PI between test and reference was -0.89 mm VAS (difference in least square [LS]

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means) with a 95% CI between -4.15 mm and 2.37 mm. Non-inferiority in PPS could be concluded, since the CI upper limit does not exceed the pre-defined non-inferiority margin of 9 mm (one sided p-value for non-inferiority <.0001).

Non-inferiority of the test product in the primary efficacy endpoint was confirmed in the FAS demonstrating the robustness of this conclusion. The difference in overall "current" PI between test and reference was 0.10 mm VAS (difference in LS means) with a 95% CI between -3.12 mm and 3.32 mm (one-sided p-value for non- inferiority <.0001).

The robustness of the trial conclusion was also shown in an additional sensitivity analysis, which evaluated a total of six additional options to calculate the primary endpoint. All six options of analysis confirmed the non-inferiority of the test product in the primary efficacy endpoint.

Although the overall "current" PI was lower for the test product (28.44 mm VAS) as compared to the reference product (29.36 mm VAS), it could not be shown that the test product is superior to the reference product based on the results of this study population, since the 95% CI (see above) exceeds 0 mm.

The mean "recalled PI during the night" (last 12 hours) over the last five days of the treatment period was 28.5 mm VAS for the test product and 29.7 mm VAS for the reference product. The mean "recalled PI during the day" (last 12 hours) over the last five days of the treatment period was 27.3 mm VAS for the test product and 27.5 mm VAS for the reference product.

The mean "current" PIs on each of the last five days of the treatment period were 27.8/29.2 (Day 1/5), 28.7/29.4 (Day 2/5), 28.9/29.3 (Day 3/5), 29.2/29.7 (Day 4/5), and 27.8/28.3 mm VAS (Day 5/5) for test and reference (test/reference), respectively. The mean "current" PIs over the last five days at each of the four scheduled time points of pain assessment during the day were 27.2/28.7 (8:00), 27.8/28.9 (12:00), 28.6/29.0 (16:00), and 27.9/28.9 mm VAS (20:00), for test and reference (test/reference), respectively.

All comparisons between test and reference in the above-mentioned secondary endpoints confirmed the non-inferiority of the test product, when applying the same non-inferiority margin as for the primary efficacy parameter of 9 mm. There were no significant differences between test and reference, although in all secondary endpoints the pain intensities during treatment with the test product were lower than the PIs during treatment with the reference product in the PPS.

The total amount of rescue medication over the whole double blind treatment period was 5.12 mg (test) and 3.82 mg (reference) as assessed in the diary and 4.7 mg (test) and 4.7 mg (reference) as assessed in the CRF. As predefined in the protocol total amount of rescue medication documented in the CRF, i.e. by the investigator, was considered more reliable and used for further calculations.

There were no significant differences in the overall effectiveness on the 4 point CAT between test and reference as assessed by the investigator or patient. In 83.9% and 64.5% of patients, treatment with the test and reference product, respectively, was "moderately effective" or "highly effective" as rated by the patient and investigator.

SAFETY RESULTS:

A total of 86 AEs were verbatim reported during this study and coded to 87 MedDRA preferred terms. Sixteen (43.2%) of 37 patients (SA set) had at least one AE in this study. The majority of AEs were mild or moderate.

Seven (19.4%) patients experienced at least one related AE while being treated with the test product (N=36) and five (13.5%) patients while being treated with the reference product (N=37). The most frequently observed related AEs were gastrointestinal and nervous system disorders commonly reported for opioids.

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There were no serious adverse events (SAEs) considered to be related to the study medication. One patient died due to respiratory and circulatory insufficiency and pulmonary embolism during the post-treatment phase, seven days after last intake of the study medication.

No AEs were reported that led to the withdrawal from the study.

No clinically significant abnormal laboratory values were documented. There was no obvious relevant trend over time for blood pressure, pulse rate, body temperature or respiratory rate.

CONCLUSION:

- The study demonstrated that once daily Hydromorphone HCl PR tablets XL were non-inferior to twice daily Palladon® retard capsules for the primary efficacy endpoint in the PPS (N=31) and the FAS (N=36).
- The robustness of the trial conclusion was additionally shown in a sensitivity analysis, which used six additional options to calculate the primary endpoint and confirmed the non-inferiority of the test product.
- Non-inferiority of once daily Hydromorphone HCl PR tablets XL to twice daily Palladon® retard capsules could further be proven for all secondary endpoints in regard to pain intensities applying the same non-inferiority margin of 9 mm as for the primary endpoint.
- Although lower pain intensities were observed for the primary efficacy endpoint and the above-mentioned secondary endpoints during treatment with the test product as compared to the reference product, superiority of the test product to the reference product could not be statistically significant confirmed in the study population.
- The study drug was well tolerated. The majority of AEs were mild or moderate. Seven (19.4%) patients experienced at least one related AE while being treated with the test product (N=36) and five (13.5%) patients while being treated with the reference product (N=37). The most frequently observed related AEs were gastrointestinal and nervous system disorders commonly reported for opioids.

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