Egalet® morphine, a once-a-day, abuse resistant opioid analgesics: a double-blind, randomized, cross-over efficacy study in cancer patients

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INTRODUCTION

Oral morphine is widely used in the management of moderate to severe pain. However, as morphine has a short half-life necessitating frequent dosing, extended release (ER) formulations have been under continuous development.

Recently a new ER formulation of morphine for once-daily dosing has been developed based on the novel proprietary Egalet® technology. The formulation is an injection molded polymer system consisting of an erodible matrix in which morphine sulfate is dispersed. The matrix is partly covered with a water-impermeable, non-erodible shell which leaves both ends of the cylindrical tablet exposed to erosion by the gastrointestinal fluid. The well-defined, fixed surface erosion area allows a tightly controlled, extended release of morphine over a period of 12 hours.

In addition, Egalet® morphine is designed to maintain its extended-release properties across a wide range of solvents including ethanol, and is resistant to physical and chemical attempts to alter the slow-release of the drug substance contained in the matrix [1].

Egalet® morphine has been shown to have a unique 24 hour plasma profile, and the potential for once-daily dosing was tested in this study.

Figure 1. Cross section of Egalet® morphine

Morphine is dispersed in a matrix (light grey) partly covered by an essentially non-erodible shell (dark grey). Morphine is released by erosion of the matrix.

STUDY DESIGN

A double-blind, randomized, cross-over Phase II study was performed to investigate the safety and efficacy of Egalet® morphine dosed once-daily compared to a standard marketed formulation, MST Continus® dosed twice-daily after two weeks of treatment. Adult patients with opioid-sensitive pain caused by active cancer and a stable strong opioid use equipotent to 30-240 mg oral morphine sulfate daily were eligible.

Patients received study medication, Egalet® morphine tablets once-daily (*Egalet a/s, Denmark*) or MST Continus® twice-daily (*Napp Pharmaceuticals, United Kingdom*). Placebo capsules were given for the evening dose during the Egalet® morphine treatment period to maintain the blind. The dose of study medication was fixed during both treatment periods. Rescue medication (immediate release morphine) was provided for use as needed for treatment of break through pain (BTP) episodes.

Patients recorded in diaries the number of doses and administration time of all medication taken and rated efficacy measurements before the scheduled morning and evening doses of study medication. A blood sample for analysis of steady-state trough plasma concentration of morphine, morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G) was collected before the morning dose of study medication on the last day of each treatment period. Samples were analyzed using a validated LC-MS/MS analysis.

RESULTS

Patients

The full analysis set (FAS) included 38 patients (24 [63.2%] males, 14 [36.8%] females): 19 in each treatment sequence group. Two patients discontinued the study after completing the first treatment period due to progression of their cancer disease. The per protocol (PP) analysis set included 34 patients with no major deviations from the protocol; all results in the PP set were comparable to the FAS.

The mean age of the patients was 57.5 years, ranging from 42 to 81 years. The most common type of cancer causing pain was malignant lung neoplasms (23.7%), followed by breast cancer (15.8%), rectal cancer (10.5%), cervix carcinoma, prostate cancer and chondrosarcoma (5.3% each).

The daily dose of study medication ranged from 30 to 210 mg/day, and all patients were fully compliant with study medication and diary completion.

Table 1. Use of rescue medication and number of BTP episodes[1] (n=37)

Endpoint	Egalet® morphine	MST Continus®	Difference (95% CI)[5]
Use of rescue medication			
Average daily number of rescue doses[2] Median (min-max)	1.0 (0.0-4.6)	0.7 (0.0-6.9)	0.07 (-0.21 ; 0.29), p=0.76
Average daily amount of rescue as % of TDD[3] Median (min-max)	8.3 (0.0-52.4)	9.5 (0.0-57.1)	0.57 (-2.38 ; 3.17), p=0.74
BTP episodes[4]			
Average daily number of BTP episodes Median (min-max)	0.7 (0.0-4.4)	0.7 (0.0-3.4)	0.00 (-0.21 ; 0.21), p=0.90

[1] Diary data from the last 7 days of each treatment period were used for the analyses
[2] One dose of rescue medication was predefined as approximately 10% of TDD. If a patient's rescue dose was different from the predefined dose, the number of rescue doses was calculated as the number of 10%-doses taken
[3] Total Daily Dose. The individual dose of ER morphine was established during a study run-in period and remained fixed for both treatment periods
[4] Break Through Pain episodes. A BTP episode was defined as any occurrence of pain that resulted in use of rescue medication. Two or more rescue doses within 2 hours were considered as one BTP episode
[5] Hodges-Lehmann estimate for difference between treatments and 95% CI, p-values were calculated using Mann-Whitney exact test for treatment effect

Efficacy

There was no difference between treatments in rescue use, BTP episodes (Table 1) or pain intensity (Figure 2), and trough plasma concentrations of morphine, M-3-G and M-6-G 24 hours after the last dose of Egalet® morphine and 12 hours after the last dose of MST Continus® were similar (Table 2). No difference was found for interference of pain with sleep, patient's impression of the study treatments (Figure 3) or patient preference for treatment.

During the 4-hour interval from 20 hours after morning dose until the next morning dose 9 subjects in each treatment group experienced BTP requiring rescue medication on at least one occasion during the 7 days of observation. The corresponding numbers for the 4-hour interval from 16 to 20 hours after morning dose were 8 patients in the Egalet® morphine group and 11 patients in the MST Continus® group.

Table 2. Trough plasma concentrations of morphine, morphine-3-glucuronide (M-3-G), and morphine-6-glucuronide (M-6-G) (n=30[1])

Analyte	Egalet® morphine	MST Continus®	Egalet® morphine / MST Continus®
	Geometric mean[2] (range)		Ratio of means[3] (95% CI)
Morphine (nmol/L)	37.4 (<0.75 ; 219.6)	37.1 (<0.75 ; 257.2)	0.99 (0.74 ; 1.33)
M-3-G (nmol/L)	1120.8 (<5 ; 9838.0)	1061.6 (<5 ; 6488.0)	1.04 (0.83 ; 1.30)
M-6-G (nmol/L)	159.8 (<1 ; 1489.0)	148.3 (<1 ; 1077.0)	1.06 (0.82 ; 1.37)

[1] Results are presented for all patients from whom a blood sample was collected. When concentrations were dose-normalized to a TDD of 100 mg/day, and for the sub-set of patients not taking any rescue medication within 4 hours prior to blood sampling (n=26), the results were comparable.
[2] In the calculation of geometric mean, values that were below the quantification limit were replaced with half of the limit. The quantification limits were 0.75 nmol/L for morphine, 5 nmol/L for M-3-G and 1 nmol/L for M-6-G.
[3] Ratio of means is based on least square mean difference estimated from ANOVA model for log-transformed data.

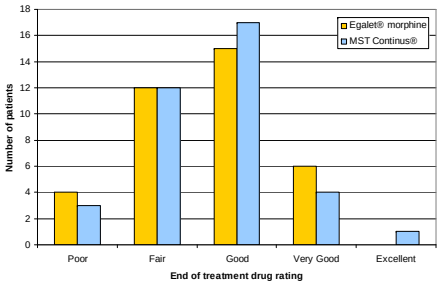
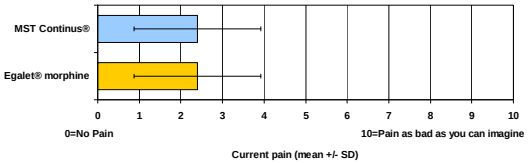


Figure 3. Patient rating of the study medication (n=37)

At the end of each treatment period patients rated their overall impression of the treatment received during the past 2 weeks on a 5-point verbal rating scale. The median assessment was "good" for both treatments with a median difference (Hodge-Lehmann) of 0.00 (95% CI -0.50 ;0.50, p=1.0).

Safety

The pattern of the overall and treatment-related AEs did not differ between treatments, and was what a clinician would reasonably expect in a population with advanced malignancy and chronic use of opioids. No difference between treatments was found for sedation ratings performed every evening on an 11-point numeric rating scale (Anchors: 0=completely alert to 10=impossible to stay awake).



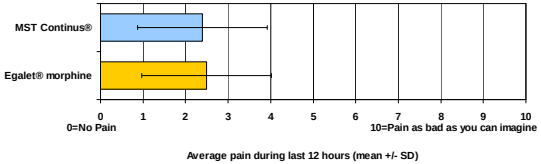


Figure 2. Pain intensity rated in the morning on an 11-point numeric rating scale (n=37)

Diary data from 7 days were averaged for analysis. ***Left:*** *Current pain intensity; median difference between treatments (Hodges-Lehmann) 0.00 (95% CI -0.10 ; 0.35), p=0.27.*
Right: *Average pain intensity during last 12 hours; mean difference between treatments (ANOVA) 0.10 (95% CI -0.13 ; 0.32), p=0.39.*

DISCUSSION

The small number of patients experiencing BTP and the absence of a trend for increasing numbers of patients with BTP episodes at the end of the dosing interval suggest that in these patients, episodes of BTP were not attributable to the analgesic effect wearing off. In addition, the similar low mean values for current pain intensity at the morning evaluation, 24 hours after the most recent exposure to Egalet® morphine versus 12 hours after the most recent exposure to MST Continus®, indicate that both treatments provided effective pain control at the end of their respective dosing intervals. In support of this therapeutic equivalency, trough plasma levels of morphine and its metabolites, 24 hours after the last dose of Egalet® morphine and 12 hours after the last dose of MST Continus®, were similar.

Based on the width of the CIs, true differences in use of rescue medication of 0.5 doses/day, and in number of BTP episodes of 0.4 episodes/day would have been captured in this study. A difference of 0.5 rescue dose/day is not considered to be clinically meaningful, and similarly a true difference below one additional BTP episode requiring a dose of rescue medication is not considered to be clinically relevant. For the pain ratings the confidence intervals for difference between treatments were well below what would be considered a clinically important difference in pain [2,3], and a difference of this level in pain intensity would not predict additional use of rescue medication [4].

CONCLUSIONS

- Egalet® morphine dosed once-daily is therapeutically equivalent to MST Continus® dosed twice-daily in cancer patients with chronic pain as shown by similar use of rescue medication, pain intensity and number of BTP episodes during the two treatment periods
- Steady-state trough plasma concentrations of morphine 24 hours after the last exposure to Egalet® morphine and 12 hours after the most recent exposure to MST Continus® were identical
- No end-of-dose failure was detected at the end of the 24-hour dosing interval for Egalet® morphine confirming the intended once-daily dosage regimen for the formulation
- The pattern of the overall and treatment-related AEs did not differ between treatments and there were no findings that raised new safety concerns

References

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[2] Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT Recommendations. J Pain 2008;9(2):105-21.

[3] Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numeric pain rating scale. Pain 2001;94:149-58.

[4] Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain 2000; 88:287-94.