Efficacy and Safety of Once-Daily Extended-Release (ER) Hydrocodone in Individuals Previously Receiving ER Morphine for Chronic Pain

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Abstract

Objectives: This post hoc analysis examined the effectiveness and safety of hydrocodone bitartrate (HYD) in patients with moderate-to-severe chronic pain who were previously taking extended-release morphine (morphine ER) for pain management.

Study Design: The primary analysis was an open-label, 12-month study.

Setting: The study was conducted in 88 sites in the United States.

Methods: The study was approved by an institutional review board. Eligible patients were enrolled and titrated to a once-daily dose of HYD 20, 40, 60, 80, or 120 mg for a 45-day period. The subgroup of patients in this report was using morphine ER prior to study entry. After achieving a stable HYD daily dose, patients entered a 12-month maintenance period during which additional dose adjustment could be made and nonopioid or short-acting opioid medications could be received. Average pain over the last 24 hours was recorded daily (on a scale of 0 to 10). Patients completed the Brief Pain Inventory (BPI) short form, which assessed pain severity and the interference of pain in daily life, every 4 weeks during the maintenance period. Safety was assessed routinely.

Results: Of the 26 patients who switched from morphine ER to HYD, 19 entered the maintenance period. At study entry, mean “average pain over the last 24 hours” was scored as 5.21. This was reduced to 3.90 by the time patients entered the maintenance phase; this level of pain control was maintained over the 12-month period, with 16 patients requiring no further HYD dose adjustment. BPI scores decreased for both pain severity and pain interference during the maintenance period. HYD was well tolerated.

Conclusions: The results of this subgroup analysis suggest that rotation from morphine ER to once-daily HYD in patients with moderate-to-severe chronic pain maintains or improves pain relief and does not increase safety concerns.

Key Words: hydrocodone, opioids, chronic pain, once-daily extended-release morphine, analgesia, abuse-deterrent properties, single-entity

INTRODUCTION

Extended-release morphine (morphine ER) is available in branded and generic form and is frequently chosen as one of the first long-acting opioids prescribed to manage patients with chronic noncancer pain. However,
morphine treatment results in inadequate efficacy and/or low tolerability for some patients.3,4 One strategy for the management of pain in these patients would be rotation from one opioid to another.5,6 The current report describes a post hoc analysis of the long-term safety and effectiveness of once-daily hydrocodone tablets in patients with moderate-to-severe chronic noncancer, non-neuropathic pain5 rotating from their existing morphine ER regimen. Hydrocodone is a semisynthetic opioid that, until recently, was only available in combination with acetaminophen or ibuprofen. This combination therapy is the most commonly prescribed opioid medication in the United States.8,9 Acetaminophen is associated with hepatotoxicity10 and ibuprofen with gastrointestinal toxicities.11 The U.S. Food and Drug Administration recommends intake of no more than 4 g/day acetaminophen and no more than 1,000 mg/day of ibuprofen when taken as part of a hydrocodone combination product,11,12 therefore limiting the dosage of hydrocodone available from these combination tablets for those in need of higher doses for analgesia.

Hydrocodone bitartrate (HYD) (Hysingla® ER; Purdue Pharma L.P., Stamford, CT, U.S.A.) is a single-entity, once-daily, ER hydrocodone bitartrate tablet recently available in the United States for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which other treatment options are inadequate.13 HYD has received labeling describing the abuse-deterrent properties of the medication that are expected to reduce its abuse and misuse.13 HYD may be a treatment option for those patients who are concerned about hepatotoxicity associated with acetaminophen, those who require opioid rotation, and those who seek once-daily dosing.

Two-phase 3 studies of HYD have been conducted to evaluate the safety and effectiveness of HYD.7,14 In a randomized, placebo-controlled, enriched enrollment study of patients with moderate-to-severe chronic low back pain, HYD demonstrated superior pain reduction after 12 weeks of double-blind treatment compared with placebo \( P = 0.0016 \).14 In a long-term, open-label study of moderate-to-severe nonmalignant and non-neuropathic chronic pain that more closely resembled pain practice in a community setting,7 patients were permitted to use short-acting opioids and nonopioid medications as supplemental analgesics to HYD; in addition, HYD dose adjustments were permitted during the maintenance period of the study. After titration of HYD, 728 patients entered the 1-year maintenance period and 410 (56%) completed it. HYD treatment resulted in improvement in pain management that was sustained throughout the year without increases in mean HYD dosing or in supplemental pain medications. HYD was generally well tolerated, the most common adverse events (AEs) being those frequently associated with mu agonist opioids.

This article evaluates the subgroup of those patients from the long-term, open-label study of HYD who had been receiving morphine ER as the primary analgesic for their chronic pain before switching to HYD.7 It is anticipated that this post hoc analysis of HYD treatment within this subgroup will provide healthcare practitioners with useful and relevant information.

METHODS

Study Design and Patients

The primary open-label study (NCT01400139) was approved by a central institutional review board prior to initiation and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practices guidelines. Before study enrollment, all potential participants provided written informed consent.

The design and patient selection have been described in detail previously.7 All data collected in this study were recorded on electronic case report forms and diaries and monitored by the study medical monitor and the study team. Briefly, at the start of the screening period of up to 14 days, the patient’s pain history and pain etiology, “average pain over the last 14 days” scores on an 11-point numerical rating scale (NRS), concomitant medication use over the prior 30 days, and vital sign measurements were recorded. In addition, a physical examination, laboratory evaluations, audiology assessments, and 3 electrocardiograms (ECGs) were performed to evaluate whether each patient met the study entry criteria.

To be eligible for inclusion in this study, male and female patients \( \geq 18 \) years of age had to have moderate-to-severe, chronic nonmalignant and non-neuropathic pain lasting several hours each day for at least 3 months prior to screening. At screening, patients’ pain conditions were required to be either controlled with a stable analgesic regimen equivalent to \( \leq 120 \) mg/day of morphine with “average pain over the last 14 days” scores \( \leq 4 \), or uncontrolled with a stable analgesic regimen...
equivalent to ≤ 100 mg/day of morphine with “average pain over the last 14 days” scores ≥ 5.

Female patients of childbearing potential were required to have a negative pregnancy test result, be nonlactating, and be willing to use contraception during the study. This post hoc analysis evaluated a subset of data from the open-label, 12-month trial, which was designed to characterize the long-term safety and effectiveness of HYD once-daily in subjects with chronic nonmalignant and non-neuropathic pain. Patients were excluded if their daily opioid regimen exceeded 120 mg morphine equivalent during the 14 days prior to screening or if they had uncontrolled gout, pseudogout, psoriatic arthritis, active Lyme disease, rheumatoid arthritis or other inflammatory arthritis, trochanteric bursitis, or ischial tuberosity bursitis. Those with a history of otologic surgery and/or pre-existing audiology conditions; a history of seizures; current uncontrolled depression or psychiatric disorder; clinically unstable cardiac disease; impaired renal or liver function; a history of alcohol, medication, or drug abuse or addiction; or a history of opioid abuse or addiction were also excluded from this study.

The post hoc analysis presented in this article evaluated a subset of data from the open-label, 12-month trial, which was designed to characterize the long-term safety and effectiveness of HYD once-daily in patients with chronic nonmalignant and non-neuropathic pain. In this analysis, patients who had previously used morphine ER before enrolling in the study were evaluated. Pain could be controlled or uncontrolled with stable analgesic regimens equivalent to up to 240 mg/day of morphine.

**Treatment**

After being screened and assessed for eligibility, enrolled patients entered into a titration period and were converted to HYD 20, 40, 60, 80, or 120 mg, with an initial dose of 50% to 75% of their total prior opioid daily dose. For example, patients who entered the study receiving oxycodone equivalents of ≤ 40, 40 to ≤ 60, 60 to ≤ 80, and > 80 mg were converted to 20, 40, 60, and 80 mg HYD, respectively. Patients who were not receiving an opioid regimen were converted to 20 mg HYD.

Patients discontinued controlled-release and long-acting opioid medications (including morphine ER), but were allowed to receive supplemental pain medication, including nonopioid analgesics, short-acting opioids (including immediate-release [IR] morphine), muscle relaxants, sedatives, and antidepressants. HYD dose adjustments were made throughout a 45-day period. If a stable HYD dose was reached (same dose for at least 7 days with acceptable pain control and tolerability), patients entered a 1-year maintenance period on the stabilized HYD dose. HYD dose adjustments during the maintenance period were permitted, as needed.

**Assessments**

Patient-reported pain intensity was assessed using an 11-point NRS in which 0 = “no pain” and 10 = “pain as bad as you can imagine.” Pain in the last 24 hours was recorded daily at approximately 8 p.m. The Brief Pain Inventory (BPI) short form of 15 items (each scored from 0 to 10) assessed pain severity and the interference by pain in daily features of life (general activities, mood, walking ability, work, relations with others, sleep, and enjoyment of life). BPI assessment was performed at baseline and every 4 weeks during the maintenance period. In addition, a treatment satisfaction questionnaire was self-administered at week 4 of the maintenance period or upon study discontinuation. Use of concomitant medication was recorded. Safety was assessed by reported AEs, clinical laboratory tests, ECGs, physical examinations, and vital sign measurements.

**Statistical Analysis**

Patients included in this post hoc analysis of morphine ER users were among those who received ≥ 1 dose of HYD during the study. Morphine ER was considered to be the patient’s primary analgesic if it was prescribed as monotherapy (or was the primary analgesic if taken concomitantly with other analgesics for pain) and was taken as a consistent analgesic regimen (ie, no “as needed” dosing). No formal statistical power calculations were considered, as it was an open-label study. The sample size of this post hoc subgroup analysis was bounded to the number of patients enrolled in the core study.

Mean weekly pain intensity was calculated from daily diaries. Because this was an open-label study, no imputation of efficacy data was performed and no formal statistical hypothesis testing was conducted. Statistically significant mean differences in weekly pain compared to baseline were determined by whether the 95% confidence intervals (CIs) around means were
overlapping. Mean BPI subscales of pain severity and pain interference were calculated, lower values representing less pain or less pain interference. Hydrocodone equivalent total opioid daily dose was calculated using conversion factors that have been previously published.13 If more than 1 opioid was used, the overall total daily dose was the sum of individual opioid daily hydrocodone equivalents.

Patient characteristics were both summarized by group and analyzed by patient. Efficacy and safety were analyzed by group.

RESULTS
Patient Characteristics and Disposition

In this post hoc analysis of the long-term safety and effectiveness study of once-daily HYD, 26 patients were identified as users of morphine ER prior to the study (Table 1). The mean (standard deviation [SD]) age among these patients was 53.0 (10.5) years and their mean body mass index was 30.0 (6.2) kg/m². The most frequent pain etiologies were back pain, intervertebral disc degeneration, and osteoarthritis. Other relevant medical conditions included other forms of pain, anxiety, depression, insomnia, and headache. At baseline, the number of patients receiving morphine once, twice, and 3 times daily were 4, 14, and 7, respectively. One patient received morphine 5 times daily. Many of these patients were receiving multiple analgesic medicines, as well as other therapies, including muscle relaxants, sedatives, and antidepressants for pain or comorbid conditions.

At screening, pain for this group of patients was rated as mostly controlled by their prior treatments. The average score of pain in the last 24 hours on a scale of 0 to 10 (SD) was 5.21 (1.8) at screening. The mean morphine ER dose (SD) at screening was 121.0 (112.4) mg daily, equivalent to 60.5 mg (28.1) of hydrocodone. For most patients, the morphine ER dosage regimen was 2 to 3 times daily (ie, every 8 to 12 hours).

Seventy-three percent of the 26 patients who switched from morphine ER to HYD were able to achieve a stable dose and proceed to the maintenance period of the study. Over the course of the titration and maintenance periods, 11 patients (42%) discontinued HYD treatment. During the dose titration period, 3 patients discontinued because of AEs, 1 for patient’s choice, and 2 for lack of therapeutic effect. One did not reach a stable dose and did not qualify for entry into the maintenance period. Of the 19 patients who entered the 52-week maintenance period, 15 (79%) completed maintenance period treatment; 1 patient discontinued for a protocol violation (receiving a reduced dose of morphine ER during the study), 1 for patient’s choice, and 2 for lack of therapeutic effect (Table 2). Of the 2 patients who discontinued the study due to lack of therapeutic effect during the maintenance period, 1 had controlled pain at baseline and 1 had severe pain at baseline and was taking oxycodone HCl as supplemental pain medication until 25 days prior to study drug discontinuation.

Reduction of Pain and Pain Interference with HYD After Switching from Morphine ER

The mean score for “average pain over the last 24 hours” was reduced from 5.21 to 3.90 during the titration period (Figure 1). Over the 52-week maintenance period of the study, additional reductions in mean pain scores (to as low as 3.14) were observed, which by the end of the period (final mean pain score 3.81) approached the level of pain reduction achieved at the end of the dose titration period. Even for patients with the least pain at the beginning of the study (ie, pain score < 4, n = 4), there was an overall mean (SD) pain score reduction from baseline of 0.29 (1.89).

During the maintenance period, mean “pain right now” scores (SD) were similar at predose (3.43 [1.91], n = 19 patients), 12 hours postdose (3.13 [2.46], n = 15 patients), and on average over the 24-hour dosing interval (3.37 [1.61], n = 19 patients) (Figure 2).

The results from the BPI show that pain severity and interference with aspects of daily life decreased in patients during the maintenance period of the trial (Table 3).

Dose Adjustments

After dose titration, the mean (SD) once-daily dose of HYD was stable during the 52-week maintenance period: 100 (32) mg at the end of titration and 99 (32) mg at the end of the maintenance period (Figure 3). The mean dose of nonstudy opioids, in hydrocodone equivalent units, decreased during conversion to HYD in the titration period. Short-acting opioids were allowed during maintenance as supplemental analgesics, and the doses of these supplemental analgesics were relatively stable at very low levels for the rest of the study, except for an increase at 9 months due to a
### Table 1. Patient Characteristics at Screening, Prior and Concomitant Pain Medications, and Starting Hydrocodone Bitartrate (HYD) Dose

| Patient no. | Sex/Age  | Pain Etiology                                                                 | Other Relevant Medical Condition          | Relevant Prior Medications*          | Relevant Concomitant Medications           | Screening Opioid Dose (mg/day) | Screening Pain Score | Screening Pain Interference Score | Starting Maintenance HYD Dose (mg/day) |
|-------------|----------|--------------------------------------------------------------------------------|-------------------------------------------|--------------------------------------|-------------------------------------------|----------------------------------|----------------------|-------------------------------|-----------------------------------|
| #1F53/29   | F/53/29  | Back pain and neck pain                                                       | None                                      | Morphine ER                          | -                                         | 120                              | 4.5                  | 5.3                           | Titration failure                  |
| #2M29/22   | M/29/22  | Back pain                                                                     | None                                      | Morphine ER                          | Trazodone, Morphine IR                   | 120                              | 4.5                  | 5.3                           | Titration failure                  |
| #3M63/31   | M/63/31  | Back pain, intervertebral disc degeneration/disorder/protrusion, spinal osteoarthris, spinal column stenosis | Insomnia, headache, arthropathy, muscle spasms, myelopathy, hypoesthesia, osteoarthris, osteomyelitis, sciatica, spinal column stenosis | Morphine ER, cyclobenzaprine, oxycodone, ibuprofen | -                                         | 120                              | 2.0                  | 1.9                           |                                  |
| #4M68/31   | M/68/31  | Intervertebral disc degeneration/protrusion, back pain, spinal osteoarthris, spinal column stenosis | Limb-crushing injury, depression, osteoarthris | Acetaminophen/hydrocodone, morphine ER, sertraline | Acetaminophen/hydrocodone, sertraline     | 144                              | 3.3                  | 4.0                           | Titration failure                  |
| #5F52/34   | F/52/34  | Back pain                                                                     | Anxiety, depression, insomnia             | Morphine ER                          | Alprazolam                               | 60                               | 4.8                  | 3.3                           | 60                                |
| #6M48/24   | M/48/24  | Back pain, spinal osteoarthris, intervertebral disc degeneration               | Anxiety, depression, insomnia             | Morphine ER, clonazepam, acetaminophen/hydrocodone, desvenlafaxine | Clonazepam, acetaminophen/hydrocodone, desvenlafaxine | 126                              | 4.3                  | 3.4                           | 120                                |
| #7M49/30   | M/49/30  | Intervertebral disc degeneration                                               | Insomnia, exostosis                       | Acetaminophen/hydrocodone, morphine, naproxen | Oxytocin, naproxen                       | 108                              | 6.9                  | 7.1                           | 120                                |
| #8F60/30   | F/60/30  | Back pain, surgery, lumbar spinal stenosis, intervertebral disc degeneration   | Depression, insomnia, tibia fracture, tendonitis, rotator cuff syndrome, sciatica | Morphine ER, amitriptyline              | Amitriptyline                            | 120                              | 6.7                  | 3.4                           | 120                                |
| #9F75/35   | F/75/35  | Back pain, intervertebral disc degeneration, spinal osteoarthris, back pain    | Anxiety, depression, insomnia             | Morphine ER, citalopram, naproxen, trazodone | Citalopram, naproxen, trazodone           | 120                              | 6.1                  | 5.1                           | Titration failure                  |
| #10M72/27  | M/72/27  | Intervertebral disc degeneration                                               | Musculoskeletal pain, headache, insomnia, neck pain, musculoskeletal chest pain | Morphine ER, hydrocodone/acetaminophen  | Oxycodone, hydrocodone/acetaminophen      | 144                              | 6.4                  | 6.0                           | 80                                |
| #11F53/26  | F/53/26  | Back pain and scoliosis                                                        | --                                        | Morphine ER, hydrocodone/acetaminophen | Acetaminophen/hydrocodone                | 120                              | 3.9                  | 1.3                           | 120                                |
| #12F39/21  | F/39/21  | Back pain                                                                     | Anxiety, pain in extremity, muscle spasms, neck pain, musculoskeletal pain | Morphine ER, hydrocodone/acetaminophen, oxycodone, ibuprofen, hydrocodone/acetaminophen | Alprazolam, cyclobenzaprine, oxycodone, hydrocodone/acetaminophen | 198                              | 5.1                  | 3.6                           | Titration failure                  |
| #13F53/30  | F/53/30  | Chronic osteomyelitis, musculoskeletal pain                                    | Cubital tunnel syndrome, depression, back pain, muscle spasms | Ibuprofen, tizanidine, morphine ER, pregabalbin | Gabapentin, acetaminophen/hydrocodone, ibuprofen, tizanidine, morphine IR, pregabalbin | 146                              | 5.3                  | 5.4                           | 120                                |
| #14M45/36  | M/45/36  | Back pain, intervertebral disc degeneration                                     | Cubital tunnel syndrome, depression, pain in extremity, neck pain, musculoskeletal pain | Morphine ER, celecoxib, ibuprofen, hydrocodone/acetaminophen | Celecoxib, ibuprofen, hydrocodone/acetaminophen | 144                              | 6.9                  | 6.6                           | 120                                |
| #15F43/46  | F/43/46  | Intervertebral disc protrusion                                                 | Major depression, insomnia                | Morphine ER                          | Oxycodone, citalopram, naproxen, ropinirole, zolpidem | 16                               | 7.0                  | 4.6                           | 120                                |
| #16F59/27  | F/59/27  | Spinal osteoarthris, back pain                                                | Major depression, insomnia                | Morphine ER, clonazepam, duloxetine, gabapentin, methocarbamol, paracetamol, naproxen, ropinirole, zolpidem | Oxycodone, clonazepam, duloxetine, methocarbamol | 200                              | 7.9                  | 6.1                           | 120                                |
| Patient no. | Sex/Age (Years)/BMI (kg/m²) | Pain Etiology | Other Relevant Medical Condition | Relevant Prior Medications* | Relevant Concomitant Medications | Screening Opioid Dose (mg/day)† | Screening Pain Score‡ | Screening Pain Interference Score§ | Starting Maintenance HYD Dose (mg/day) |
|------------|-----------------------------|--------------|---------------------------------|-----------------------------|---------------------------------|-------------------------------|-------------------|-----------------------------|----------------------------------|
| #17M/53/35 | Back pain                   | Depression, insomnia, arthralgia, migraine | Morphine ER, oxycodone, mirtazapine, quetiapine, bupropion | –                            | Hydrocodone/acetaminophen, metaxalone, lidocaine | 150              | 7.7              | 6.1                        | Titration failure               |
| #18F/58/34 | Osteoarthritis and back pain| Muscle spasms | Morphine ER, metaxalone, lidocaine | Hydrocodone/acetaminophen, duloxetine, Thomapyrin N, methocarbamol, tizanidine, lidocaine | 60                   | 6.9              | 3.1                        | 80                               |
| #19M/52/33 | Back pain, intervertebral disc degeneration | None | Morphine ER | Morphine ER, as needed | 46                   | 1.5              | 1.3                        | 60                               |
| #20M/65/29 | Back pain                   | Headache, muscle spasms, osteoarthritis, sciatica | Hydrocodone/acetaminophen, morphine, duloxetine, Thomapyrin N, methocarbamol, tizanidine, lidocaine | 136              | 5.7              | 3.6                        | 120                              |
| #21F/62/43 | Back pain                   | Neck pain, pain in extremity, headache, arthralgia, muscle spasms, osteoarthritis, sciatica | Morphine ER | –                            | 20                   | 6.6              | 5.4                        | 20                               |
| #22F/44/26 | Neck pain                   | Arthralgia, anxiety, depression, musculoskeletal pain, back pain, muscle spasms | Morphine ER, oxycodone/acetaminophen, tizanidine, meloxicam | Oxydodone/acetaminophen, tizanidine, meloxicam | 210              | 3.8              | 1.3                        | Titration failure               |
| #23F/56/23 | Back pain                   | Anxiety, depression, osteoarthritis | Morphine ER, ibuprofen, amitriptyline, Thomapyrin N, alprazolam, hydrocodone/acetaminophen | Ibuprofen, amitriptyline, Thomapyrin N, alprazolam, hydrocodone/acetaminophen | 148              | 4.4              | 2.0                        | 120                              |
| #24F/53/20 | Intervertebral disc degeneration | Migraine, osteoarthritis | Morphine ER, chlorzoxazone | Ibuprofen, chlorzoxazone | 30                   | 7.4              | 5.6                        | 60                               |
| #25M/59/28 | Back pain, intervertebral disc degeneration | Headache | Morphine ER, hydrocodone/acetaminophen, naproxen | Morphine ER, hydrocodone/acetaminophen, naproxen | 114              | 5.0              | 3.1                        | 120                              |
| #26F/62/31 | Back pain                   | Depression, spinal laminectomy, osteoarthritis | Morphine ER, carisoprodol, alprazolam, ibuprofen | Morphine IR, carisoprodol, alprazolam, ibuprofen | 120              | 2.2              | 1.4                        | 120                              |

BMI, body mass index; ER, extended-release; IR, immediate-release.
*Prior medications were taken within 30 days of screening visit.
†Morphine equivalent.
‡11-point numerical rating scale (0 = “no pain,” 10 = “pain as bad as you can imagine”).
§Brief Pain Inventory Short Form–Pain Interference Score.
temporary increase in the dose of 1 patient (see Figure 3). Nine patients (35%) were receiving supplemental treatment with the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen or naproxen at baseline and during the titration period; all were discontinued by month 6 of the maintenance period.

Sixteen patients (84%) had no change in HYD dose during the maintenance period of the trial (Figure 4). A single-level dose increase (eg, HYD dose increased from 80 to 120 mg) occurred in 2 patients (10.5%), and a dose decrease occurred in 1 patient (5.3%).

### Treatment Satisfaction Questionnaire

Of 19 patients who entered the maintenance period, 18 completed the treatment satisfaction questionnaire. Of these 18, 16 (89%) described themselves as satisfied with the study drug in comparison with the previous analgesic regimen (ie, morphine ER primarily dosed 2 or 3 times daily), and the same proportion (89%) found HYD to be easy to use (Table 4). Seventeen patients (94%) were satisfied with the frequency of use. All 18 patients found HYD treatment to be convenient and considered the planning of HYD use to be easy.

### Treatment-Emergent AEs

Treatment-emergent, opioid-related AEs experienced by more than 1 patient during either the titration or maintenance period were constipation, insomnia, nausea, and dizziness (Table 5). One patient with a prior history of rhabdomyolysis experienced a treatment-emergent serious AE of elevated creatine phosphokinase (worsening rhabdomyolysis) during the study; the event was considered by the investigator not to be related to the study drug; the patient recovered from the event.

### DISCUSSION

Morphine, a naturally occurring opioid present in opium, has been used for hundreds of years as a potent analgesic. Morphine ER continues to be among the

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**Table 2. Summary of Patient Disposition and Reasons for Discontinuation from Hydrocodone Bitartrate (HYD) for Patients Switching from Extended-Release Morphine**

|                  | Dose Titration Period | Maintenance Period | Overall Treatment Period |
|------------------|-----------------------|--------------------|-------------------------|
|                  | (N = 26)              | (N = 19)           | (N = 26)                |
| Completed period on HYD | 19 (73)               | 15 (79)            | 15 (58)                 |
| Discontinued study |                      |                    |                         |
| Reason for discontinuation |                    |                    |                         |
| Adverse event    | 3 (12)                | 0                  | 3 (12)                  |
| Patient's choice | 1 (4)                 | 1 (5)              | 2 (8)                   |
| Lost to follow-up| 0                     | 0                  | 0                       |
| Lack of therapeutic effect | 2 (8)                | 2 (11)             | 4 (15)                  |
| Confirmed or suspected diversion | 0                    | 0                  | 0                       |
| Administrative   | 0                     | 1 (5)              | 1 (4)                   |
| Did not qualify for maintenance period | 1 (4)                | NA                | 1 (4)                   |

*N*, number of patients in the safety population; *n*, number of patients with data; NA, not applicable.

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![Figure 1. Mean "average pain over the last 24 hours." DT, dose titration; ER, extended-release; HYD, hydrocodone bitartrate; SE, standard error.](image-url)
most frequently prescribed ER opioids in the United States, although for some patients, morphine treatment results in inadequate efficacy and/or low tolerability. A possible strategy for management of pain in these patients would be rotation from one opioid to another. The current report describes post hoc analysis of a study of the long-term safety and effectiveness of HYD (single-entity, once-daily HYD tablets with abuse-deterrent properties) in adults with moderate-to-severe chronic noncancer, non-neuropathic pain. Twenty-six patients had received morphine ER prior to study entry. The patients were characteristic of those seen in clinical practice, many experiencing, for example, anxiety, depression, and/or insomnia in addition to chronic pain.

Average pain score at screening among these patients was 5.2. Switching from morphine ER to HYD resulted in a reduction in average pain score at the end of the titration period (3.9) that was maintained below this level throughout the 52-week maintenance period. The severity of pain and the interference by pain in features of daily living, as assessed by the BPI scale, were also reduced. Similar reductions in pain scores and pain interference scores had occurred in the study overall.

Table 3. Brief Pain Inventory (BPI) Short Form

| Mean Score                          | Baseline (N = 26) | Change from Baseline* (N = 19) |
|-------------------------------------|-------------------|--------------------------------|
| BPI                                 | 4.57              | -1.47                          |
| BPI pain severity subscale          | 3.99              | -1.12                          |
| BPI pain interference subscale      | 5.15              | -1.82                          |

N, number of patients in the safety population.
*Change from baseline of overall maintenance average.

Figure 2. Mean “pain right now” scores recorded immediately prior to each daily dose and at 12 hours postdose and mean “average pain over last 24 hours” score during the maintenance period (dashed line). Error bars represent the standard deviation.

![Figure 3](image3.png)

**Figure 3.** Average daily dose of hydrocodone bitartrate (HYD) and supplemental opioids. The mean dose for nonstudy opioid analgesics is reported in oxycodone equivalents. SE, standard error.
Hydrocodone bitartrate consistently provided analgesia throughout the 24-hour dosing interval. Mean “pain right now” patient-reported scores were similar immediately prior to dosing and approximately 12 hours later. These scores were also consistent with the mean “average pain over the last 24 hours” score. Notably, morphine was more frequently dosed in the majority of patients compared with once-daily HYD. The starting HYD dosage was based on calculated opioid equivalents of the previous treatments. For this subgroup of patients with morphine as their primary baseline opioid analgesic, the mean HYD dosage was higher than that seen in the overall study population, both at the start and end of the titration period (51 and 96 mg/day, respectively, compared with 28 and 61 mg/day, respectively).

Although the study protocol required discontinuation of ER and long-lasting opioids, other nonstudy supplemental IR opioid use was permitted. However, nonstudy supplemental opioid and NSAID use decreased from baseline among this subgroup of patients, as it had in the overall study population, indicating that the patients’ pain was well managed with HYD treatment.

A large proportion (73%) of the previous users of morphine ER was able to achieve a stable dose of HYD and enter the maintenance period, and 79% of these completed the trial. Of the 2 discontinuations during the maintenance period for lack of therapeutic effect, 1 might have been influenced by the patient’s discontinuation of concomitant oxycodone a few weeks prior to the discontinuation of HYD. That there were no discontinuations during the maintenance period due to AEs supports the general tolerability of HYD.

High levels of satisfaction with HYD and comfort with HYD use were demonstrated in the treatment satisfaction survey, also in parallel with the study as a whole. In addition, the most frequently reported AEs

### Figure 4
Hydrocodone bitartrate (HYD) dose adjustments during the maintenance period of the study. 1 level increase = a single-level dose increase (eg, HYD dose increased from 80 to 120 mg).

### Table 4. Treatment Satisfaction Questionnaire

| Question Number: Category Answered | Total (N = 19) n (%) |
|-------------------------------------|----------------------|
| 1: Satisfaction with study drug, NP | 18 (89) |
| Satisfied to extremely satisfied    | 16 (89) |
| Dissatisfied to extremely dissatisfied | 2 (11) |
| 2: Ease of study drug use to treat pain, NP | 18 (89) |
| Easy to extremely easy             | 16 (89) |
| Difficult to extremely difficult   | 2 (11) |
| 3: Convenience of study drug to treat pain, NP | 18 (89) |
| Convenient to extremely convenient | 18 (100) |
| 4: Overall drug satisfaction managing pain, NP | 18 (89) |
| Satisfied to extremely satisfied   | 16 (89) |
| Dissatisfied to extremely dissatisfied | 2 (11) |
| 5: Satisfaction with frequency of use, NP | 18 (94) |
| Satisfied to extremely satisfied   | 17 (94) |
| Dissatisfied to extremely dissatisfied | 1 (6) |
| 6: Ease of planning study drug use, NP | 18 (100) |
| Easy to extremely easy             | 18 (100) |
| Difficult to extremely difficult   | 0 |

### Table 5. Opioid-Related Treatment-Emergent Adverse Events (TEAEs)

| MedDRA System Organ Class Preferred Term | Total (N = 26) n (%) |
|------------------------------------------|----------------------|
| Any TEAE*                                 | 14 (54) |
| Gastrointestinal disorders               | 5 (19) |
| Constipation                             | 3 (12) |
| Nausea                                   | 2 (8) |
| Dry mouth                                | 1 (4) |
| Vomiting                                 | 1 (4) |
| General disorders and administration site conditions | 2 (8) |
| Fatigue                                  | 1 (4) |
| Edema peripheral                         | 1 (4) |
| Injury, poisoning, and procedural complications | 1 (4) |
| Fall                                     | 1 (4) |
| Nervous system disorders                 | 4 (15) |
| Dizziness                                | 2 (8) |
| Headache                                 | 1 (4) |
| Somnolence                               | 1 (4) |
| Psychiatric disorders                    | 4 (15) |
| Insomnia                                 | 4 (15) |
| Skin and subcutaneous tissue disorders   | 1 (4) |
| Hyperhidrosis                            | 1 (4) |

*Any TEAE represents the total number of patients with a TEAE in any of the treatment periods. Multiple occurrences of the same adverse event in 1 individual are counted only once.
were consistent with those commonly associated with the use of opioid analgesics.4

All assessments used in this study were standard, widely used, and generally recognized as reliable, accurate, and relevant. Additional measures for safety and effectiveness of therapy will depend on new research and validation of instruments.

This analysis has the limitations of being post hoc, covering a small number of individuals, and reporting open-label treatment. However, the results closely mirror those of the large, long-term study that had a design that mimicked, insofar as possible, actual pain practice in community settings.

In conclusion, the results of this subgroup analysis suggest that rotation from morphine ER to once-daily HYD in patients with moderate-to-severe chronic pain maintains or improves pain relief and does not increase safety concerns. In this population, treatment with HYD was shown to provide sustained pain relief without requiring dosage increase.

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