

A long-term, open-label safety study of single-entity hydrocodone bitartrate extended release for the treatment of moderate to severe chronic pain

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Objective: To evaluate the long-term safety, tolerability, and effectiveness of single-entity extended-release hydrocodone in opioid-experienced subjects with moderate to severe chronic pain not receiving adequate pain relief or experiencing intolerable side effects from their current opioid.

Methods: This multicenter, open-label study started with a conversion/titration phase (≤ 6 weeks) where subjects ($n=638$) were converted to individualized doses (range 20–300 mg) of extended-release hydrocodone dosed every 12 hours, followed by a 48-week maintenance phase ($n=424$). The primary objective (safety and tolerability) and the secondary objective (long-term efficacy as measured by change in average pain score; 0= no pain, 10= worst imaginable pain) were monitored throughout the study.

Results: Subjects were treated for a range of chronic pain etiologies, including osteoarthritis, low back pain, and neuropathic and musculoskeletal conditions. The mean hydrocodone equivalent dose at screening was 68.9 ± 62.2 mg/day and increased to 139.5 ± 81.7 mg/day at the start of the maintenance phase. Unlimited dose adjustments were permitted at the investigator's discretion during the maintenance phase, reflecting typical clinical practice. No unexpected safety issues were reported. Common adverse events during the conversion/titration and maintenance phases, respectively, were constipation (11.3% and 12.5%), nausea (10.7% and 9.9%), vomiting (4.1% and 9.7%), and somnolence (7.7% and 4.2%). Four deaths occurred during the study; all were considered unrelated to treatment. One subject died 13 months after the study ended. From the start to end of the conversion/titration phase, 84% of subjects had a clinically meaningful improvement in average pain score ($\geq 30\%$ improvement), and the mean average pain scores remained stable through the maintenance phase.

Conclusion: This single-entity, extended-release formulation of hydrocodone was generally safe, well tolerated, and effective in reducing chronic pain for 48 weeks. This formulation provides a new option for patients experiencing chronic pain, especially those who are taking immediate-release hydrocodone and have concerns about liver toxicity due to acetaminophen.

Keywords: opioids, long-term, chronic pain, hydrocodone, extended-release, single-entity

Introduction

Chronic pain, commonly defined as pain persisting past the normal time of healing,¹ affects an estimated 100 million adults in the US, and its annual financial impact is estimated between \$560 billion and \$635 billion (in 2010 dollars).² Typically, chronic pain is initially treated with nonopioids such as acetaminophen (APAP) or ibuprofen. If the pain persists, the treatment may progress to opioids: eg, oxycodone, morphine, or hydrocodone (HC). HC is similar in potency to oxycodone and morphine and less potent than hydromorphone and fentanyl.^{3,4} Until recently, HC was only available

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as an immediate-release (IR) product in combination with a nonopioid. In fact, HC/APAP combination products for the treatment of pain were the most commonly prescribed medications in the US from 2009 to 2013, with between 129.2 million and 136.7 million prescriptions dispensed per year.⁵ However, some patients not achieving adequate pain relief may require high doses of HC, and toxicities associated with the nonopioid component may limit the total daily dose of the combination formulation.⁶ APAP is associated with liver toxicity,⁷ and ibuprofen is associated with increased risks of serious cardiovascular and gastrointestinal adverse events (AEs).⁸

Hydrocodone bitartrate extended release (HC-ER, Zohydro[®] ER; Zogenix, Inc., Emeryville, CA, USA) is the first US Food and Drug Administration-approved single-entity ER formulation specifically developed for the management of chronic pain severe enough to require around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.⁹ A 12-week, randomized, placebo-controlled study of HC-ER demonstrated that HC-ER resulted in significantly better pain relief than placebo in opioid-experienced patients with chronic low back pain.¹⁰ To further the understanding of HC-ER, the study presented here describes the long-term safety, tolerability, and effectiveness of HC-ER in opioid-experienced subjects with moderate to severe chronic pain not achieving adequate pain relief from their current opioid treatment.

Materials and methods

Overall design

This multicenter (56 US sites), open-label study was conducted from June 2, 2010 to December 22, 2011 and consisted of a conversion/titration (C/T) phase of ≤ 6 weeks followed by a 48-week maintenance phase in opioid-experienced subjects with chronic pain. The primary objective of the study was to evaluate the long-term safety and tolerability of HC-ER.

Study population

Male or female subjects aged 18–75 years were included if they had been diagnosed with chronic pain (defined as moderate to severe pain for ≥ 3 months' duration prior to screening), had been taking opioids equivalent to 45 mg morphine/day for ≥ 5 days/week for the month before screening, and, in the investigator's opinion, needed continuous, around-the-clock opioid treatment. Subjects were excluded if they had a history of illicit drug or alcohol abuse in the past 5 years; any history of opioid abuse; a history of intolerance

to HC or APAP; conditions that, in the investigator's opinion, could interfere with pain assessment or ability to take HC-ER (examples include chronic carbon dioxide retention or respiratory depression, chronic constipation, gastroparesis, inflammatory bowel disease, and active seizure disorder); uncontrolled blood pressure (defined as sitting systolic blood pressure > 180 mmHg or < 90 mmHg and/or sitting diastolic blood pressure > 120 mmHg or < 50 mmHg); body mass index of > 45 kg/m²; clinically significant abnormality in blood chemistry (including serum glutamic oxaloacetic transaminase/aspartate aminotransferase or serum glutamic pyruvic transaminase/alanine aminotransferase ≥ 2.5 times the upper limit of the reference range or serum creatinine > 2 mg/day), hematology, urinalysis, or other laboratory values at the discretion of the investigator; a Hospital Anxiety and Depression Scale (HADS) score of > 12 in either depression or anxiety subscales; or a history of poorly controlled psychiatric disorder.

Treatments

HC-ER was supplied as 10, 20, 30, 40, and 50 mg capsules. The current opioid dose was converted to the recommended dose of HC-ER using an opioid conversion table,¹¹ then this value was reduced by approximately 20%–30% at the discretion of the investigator to determine the starting dose of HC-ER. Dosing throughout the study was twice daily at 12-hour intervals (q12h).

During the C/T phase, HC-ER doses were titrated from the initial HC-ER dose in increments of 20 mg/day (ie, 10 mg q12h) every 3–7 days until a stabilized dose had been achieved. A stabilized dose was achieved when a subject tolerated the treatment well and had an average 24-hour pain score of ≤ 4 on the numerical rating scale (0= no pain, 10= worst pain) during the 7 days prior to entering the maintenance phase and no more than two doses of rescue medication (HC-IR/APAP 5/500 mg) on any day. Subjects also were allowed one downtitration for reasons of tolerability during the C/T phase. Subjects who could not achieve a stabilized dose in 6 weeks were discontinued from the study.

Upon reaching a stabilized dose, subjects entered the maintenance phase and continued HC-ER at their stabilized dose. During the maintenance phase, the dose of HC-ER was permitted to be adjusted up or down at any study visit at the investigator's discretion, for reasons of efficacy or tolerability, without a limit to the number of adjustments. If a dose adjustment was necessary, the investigator adjusted the HC-ER dose first and then could add

nonopioid analgesics in a manner consistent with standard practice. Subjects were permitted rescue medication of one to two tablets of HC-IR/APAP 5/500 mg every 4–6 hours with a maximum of two tablets per day for breakthrough pain. Patients recorded the use of rescue medication daily in their study diary.

Safety

Subjects received a complete physical examination at screening and again at week 48 or early termination. Blood chemistry, hematology, urinalysis, and drug screen were analyzed at screening, day 1, week 12, week 36, and week 48 or early termination. Vital signs were collected at screening, every week during the C/T phase (days –42, –35, –28, –21, and –7), day 1, and every 4 weeks during the maintenance phase (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48). AEs were monitored throughout the study. Subjects received a follow-up phone call 14 days after the end of the study (week 48 or early termination) to collect information regarding ongoing AEs or new serious AEs (SAEs) that occurred during this time period.

Drug accountability

During the study, the numbers of HC-ER capsules and rescue medication tablets dispensed and returned were recorded and compared with the subject's diary to account for all study drug dispensed. When study medication could not be 100% accounted for, at either the site or subject level, it was recorded as an administrative SAE, and procedures according to the federal and state Drug Enforcement Agency were followed. The study medical monitor reviewed every case where study medication was not 100% accounted for to determine whether the subject was eligible to continue in the study. In every instance, the most conservative assessment was taken, in that missing or unaccounted for medication without a reasonable cause was considered a diversion, including misuse of study/rescue medication. The investigator and medical monitor jointly determined whether a subject could continue in the study.

Effectiveness

The secondary objective was to evaluate the long-term effectiveness of HC-ER. At screening, the Brief Pain Inventory (BPI), HADS, Oswestry Disability Index (ODI), and Subject Global Assessment of Medication (SGAM) were completed.^{12–15} During the C/T phase, pain scores were recorded by the subject in their daily diary and reviewed during the weekly clinical visit. During the maintenance phase,

pain scores, BPI, HADS, ODI, and SGAM were assessed in-clinic every 4 weeks for 48 weeks.

Statistical analyses

All safety, tolerability, and efficacy measures were summarized descriptively. No inferential statistical testing was planned or performed. All patients who took at least one dose of the study medication were included in the analysis. Missing efficacy data (ie, pain score, BPI, HADS, ODI, SGAM) were not imputed. Subjects who demonstrated a $\geq 30\%$ reduction in average pain score from screening to week 48 were classified as responders, whereas other subjects, including those who terminated the study early, were classified as nonresponders.

Study ethics

This study was approved by the Institutional Review Board at each study site and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The study drug, a schedule II controlled substance, was handled in compliance with all federal and state Drug Enforcement Agency regulations. All patients provided informed written consent.

Results

Study population

A total of 638 subjects were enrolled in the study; 424 subjects (66%) completed the C/T phase and continued to the maintenance phase, and 285 (67%) of the subjects who entered the maintenance phase completed the study (Figure 1). Demographics and clinical characteristics at screening were similar between subjects in the C/T and maintenance phases (Table 1). The mean HC equivalent (\pm standard deviation [SD]) was 68.9 ± 62.2 mg/day at screening for the patients in the maintenance phase. The most frequently reported prior opioid medications in the C/T phase population were HC/APAP (53.0%), oxycodone (19.1%), oxycodone/APAP (15.2%), morphine (14.6%), and tramadol (13.2%). The most common underlying pain conditions included osteoarthritis, chronic low back pain, neuropathic pain, and musculoskeletal pain (Table 1). Almost half of the patients (40.6%) reported a history of depression, with similar proportions between those who entered (39.4%) or did not enter (43.0%) the maintenance phase. The following non-pain-related medical history or conditions were reported by $\geq 10\%$ of the subjects enrolled in the study: hypertension (49.1%), depression (40.6%), insomnia (38.7%), anxiety (35.7%), gastroesophageal

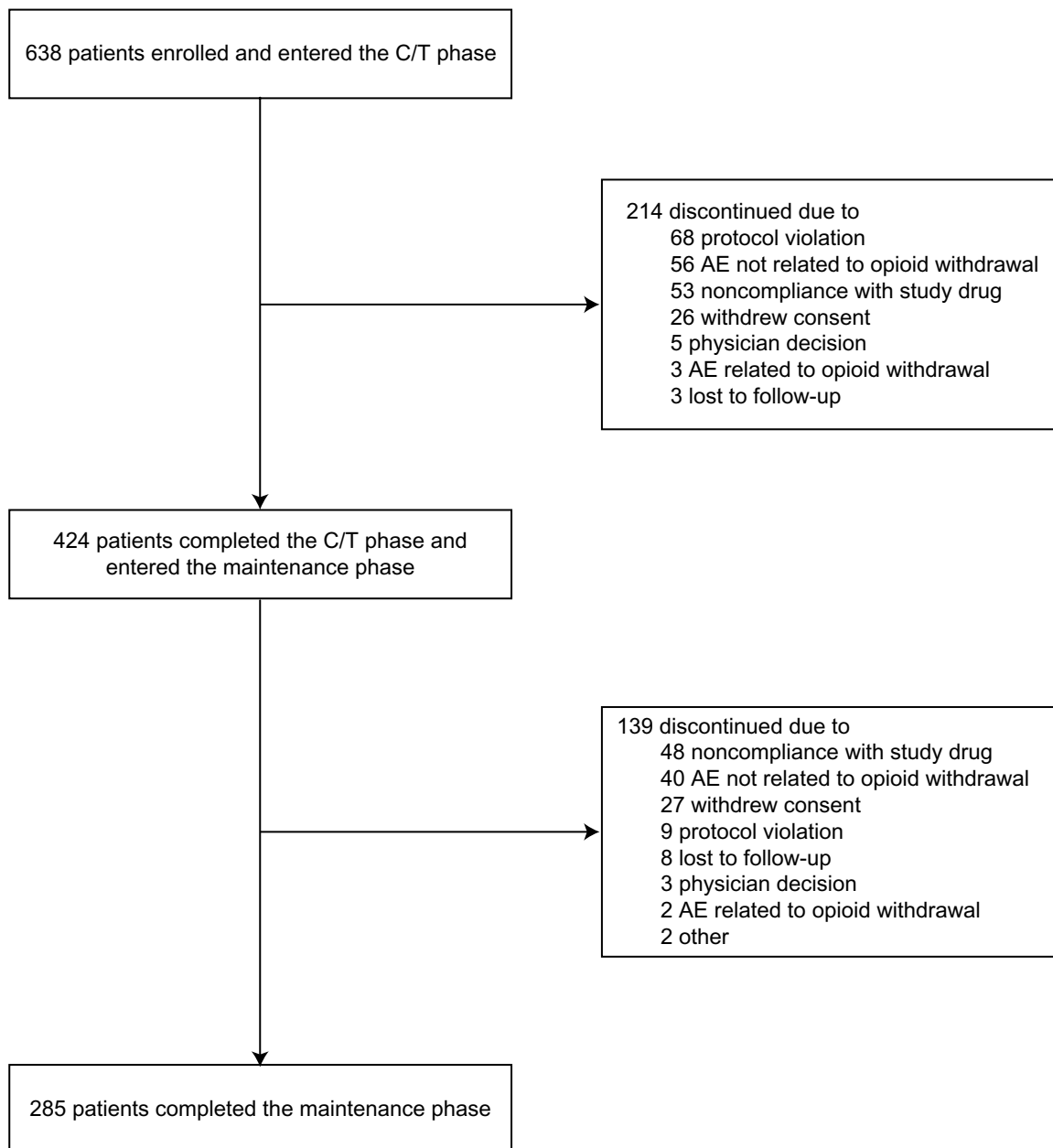


Figure 1 Disposition of patients in the study.

Notes: Noncompliance includes subjects unable to account for 100% of the HC-ER or rescue medication. Protocol violations include subjects who failed to achieve a stable dose of HC-ER during the C/T phase.

Abbreviations: HC-ER, hydrocodone bitartrate extended release; C/T, conversion/titration; AE, adverse event.

reflux disease (27.3%), hysterectomy (22.4%), constipation (21.8%), headache (21.5%), drug hypersensitivity (20.4%), seasonal allergy (19.3%), spinal fusion surgery (11.8%), migraine (14.3%), hypercholesterolemia (14.6%), hyperlipidemia (11.9%), type 2 diabetes mellitus (11.4%), blood cholesterol increased (11.1%), asthma (10.8%), and postmenopause (10.7%). Of the subjects enrolled, three (1.4%) subjects discontinued due to opioid withdrawal, and none of the subjects discontinued due to uncontrolled pain during the C/T phase.

Treatment

The mean duration of exposure to HC-ER for subjects who entered the maintenance phase ($n=424$) was 300 ± 112 days, including 33 ± 10 days in the C/T phase and 267 ± 113 days during the maintenance phase. The subjects who entered the maintenance phase demonstrated a wide range of stabilized daily doses of HC-ER at the end of the C/T period (range, 40–600 mg; median, 120 mg/day; mean \pm SD, 139.5 ± 81.7 mg/day) (Figure 2). Of the 285 subjects who completed the study, 109 (38%) subjects had no change or

Table 1 Demographic and clinical characteristics at screening for patients who entered the C/T and maintenance phases

| | C/T phase | Maintenance phase |
|-----------------------------------|-----------------|-------------------|
| N | 638 | 424 |
| Age, years | | |
| Mean \pm SD | 50.9 \pm 10.9 | 50.7 \pm 11.0 |
| Range | 20–75 | 20–75 |
| Sex, n (%) | | |
| Female | 360 (56.4) | 239 (56.4) |
| Race, n (%) | | |
| White | 518 (81.2) | 337 (79.5) |
| African American | 107 (16.8) | 77 (18.2) |
| Asian | 1 (0.2) | 1 (0.2) |
| American Indian or Alaskan native | 3 (0.5) | 2 (0.5) |
| Other | 9 (1.4) | 7 (1.7) |
| Average pain score | | |
| Mean \pm SD | 6.4 \pm 1.7 | 6.4 \pm 1.8 |
| Range | 1–10 | 1–10 |
| Pain type, ^a n (%) | | |
| Chronic low back pain | 299 (46.9) | 198 (46.7) |
| Osteoarthritis | 133 (20.8) | 97 (22.9) |
| Fibromyalgia | 55 (8.6) | 25 (5.9) |
| Neuropathic pain | 28 (4.4) | 18 (4.2) |
| Rheumatoid arthritis | 14 (2.2) | 8 (1.9) |
| Diabetic neuropathy | 5 (0.8) | 3 (0.7) |
| Cancer-related pain | 1 (0.2) | 1 (0.2) |
| Other ^b | 210 (32.9) | 139 (32.8) |

Notes: Data are n (%) or mean \pm SD. ^aIndividual subjects could have had more than one underlying condition; ^bincludes various nonneuropathic and musculoskeletal pain types.

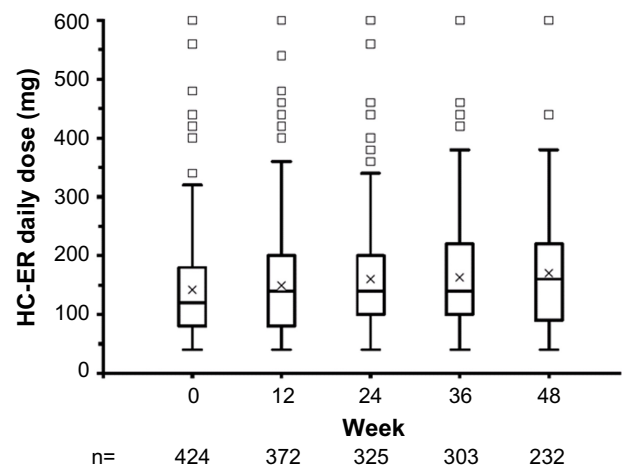
Abbreviations: C/T, conversion/titration; SD, standard deviation.

a decrease in the HC-ER dose from the start to the end of the maintenance phase, and 176 (62%) subjects had an increase in the HC-ER dose during the same period. An increase in the HC-ER dose of $\geq 100\%$ occurred in 29 (10%) of the subjects from the start to the end of the maintenance phase. No relationships were noted between the dose of HC-ER over time and reasons for study discontinuation.

During the C/T phase, the mean total daily dose of the rescue medication (for the HC component only) was 10.4 \pm 5.4 mg HC (range 0–21.4 mg) and 12.7 \pm 7.3 mg HC (range 0–50 mg) for subjects who entered and did not enter the maintenance phase, respectively. During the maintenance phase, the mean total daily dose of the rescue medication was 6.7 \pm 3.8 mg HC and about 670 mg APAP with a range of 0–22 mg HC and about 0–2,200 mg APAP).

Safety

The most common AEs reported during the C/T and maintenance phases are listed in Table 2. AE-related discontinuations in the C/T phase (occurring in three or more subjects) were nausea (ten subjects [2%]), somnolence (nine [1.4%]),

**Figure 2** HC-ER dose over time during the maintenance phase.

Notes: The \times and horizontal line indicate mean and median daily dose, respectively. The rectangle and whiskers indicate the 25th and 75th quartiles and 1.5 times interquartile range, respectively. The open squares are outliers.

Abbreviation: HC-ER, hydrocodone bitartrate extended release.

insomnia (seven [1.1%]), lethargy (seven [1.1%]), headache (seven [1.1%]), vomiting (four [0.6%]), constipation (three [0.5%]), and peripheral edema (three [0.5%]). During the maintenance phase, the most frequent AE-related discontinuations were due to constipation, upper abdominal pain, and cognitive disorder, each reported by two (0.5%) subjects. Most AEs were of mild to moderate severity; severe AEs occurred in 12% and 24% of subjects during the C/T and maintenance phases, respectively. The most frequently observed severe AEs during the maintenance phase were back pain (2.4%), arthralgia (1.7%), constipation (1.7%), and headache (1.4%).

Four subjects died during the maintenance phase, none during the C/T phase (Table 2). Two subjects died because of chronic illness (one stage IV non-small-cell lung cancer, one atherosclerotic coronary artery disease). One subject with a history of depression and anxiety died by suicide via carbon monoxide poisoning and one subject died after an influenza-like illness due to mixed drug toxicity (oxycodone, methadone, benzodiazepines, and trace HC). None of these deaths was considered related to the study drug. A fifth subject died 13 months after the study by suicide due to mixed drug toxicity (hydromorphone, HC, dihydrocodeine, trazodone, and ethanol), and hoarding of HC-ER may have been involved. Sixteen (2.5%) SAEs occurred during the C/T phase (Table 2); all occurred once each except noncardiac chest pain, which was reported twice. During the maintenance phase, 51 (12%) subjects reported one or more SAEs (Table 2). The most frequent SAEs were chronic obstructive pulmonary disease (five [1.2%]), osteoarthritis (four [0.9%]), pneumonia (three [0.7%]), small intestinal obstruction (two [0.5%]), intentional

Table 2 Number (%) of patients with treatment-emergent adverse events for patients who entered the C/T and maintenance phases

| | C/T phase | | | Maintenance phase |
|--|--|--|------------|----------------------|
| | Subjects who entered the maintenance phase | Subjects who did not enter the maintenance phase | Total | |
| N | 424 | 214 | 638 | 424 |
| Overall | | | | |
| At least one AE | 242 (57.1) | 162 (75.7) | 404 (63.3) | 354 (83.5) |
| At least one drug-related AE | 147 (34.7) | 93 (43.5) | 240 (37.6) | 130 (30.7) |
| At least one serious AE | 6 (1.4) | 10 (4.7) | 16 (2.5) | 51 (12.0) |
| At least one drug-related serious AE | 0 | 1 (0.5) | 1 (0.2) | 2 (0.5) |
| AE leading to discontinuation | 7 (1.7) ^a | 59 (27.6) | 66 (10.3) | 34 (8.0) |
| Serious AE leading to discontinuation | 0 | 5 (2.3) | 5 (0.8) | 8 (1.9) |
| Drug-related serious AE leading to discontinuation | 6 (1.4) ^a | 45 (21.0) | 51 (8.0) | 0 |
| Death | 0 | 0 | 0 | 4 (0.9) ^b |
| Adverse events in ≥5% of subjects in either phase | | | | |
| Constipation | 54 (12.7) | 18 (8.4) | 72 (11.3) | 53 (12.5) |
| Back pain | 4 (0.9) | 5 (2.3) | 9 (1.4) | 47 (11.1) |
| Nausea | 36 (8.5) | 32 (15.0) | 68 (10.7) | 42 (9.9) |
| Vomiting | 10 (2.4) | 16 (7.5) | 26 (4.1) | 41 (9.7) |
| Arthralgia | 4 (0.9) | 5 (2.3) | 9 (1.4) | 33 (7.8) |
| Headache | 32 (7.5) | 16 (7.5) | 48 (7.5) | 29 (6.8) |
| Urinary tract infection | 3 (0.7) | 3 (1.4) | 6 (0.9) | 28 (6.6) |
| Fall | 3 (0.7) | 5 (2.3) | 8 (1.3) | 25 (5.9) |
| Upper respiratory tract infection | 6 (1.4) | 1 (0.5) | 7 (1.1) | 25 (5.9) |
| Nasopharyngitis | 10 (2.4) | 1 (0.5) | 11 (1.7) | 24 (5.7) |
| Anxiety | 5 (1.2) | 3 (1.4) | 8 (1.2) | 23 (5.4) |
| Sinusitis | 6 (1.4) | 3 (1.4) | 9 (1.4) | 23 (5.4) |
| Insomnia | 13 (3.1) | 11 (5.1) | 24 (3.8) | 21 (5.0) |
| Somnolence | 31 (7.3) | 18 (8.4) | 49 (7.7) | 18 (4.2) |

Notes: ^aAEs that led to discontinuation were attributed to the study phase in which the event began (eg, seven subjects discontinued in the maintenance phase due to an AE that began in the C/T phase); ^bfour subjects died: one stage IV non-small-cell lung cancer, one atherosclerotic coronary artery disease, one suicide via carbon monoxide poisoning (history of depression), and one influenza-like illness due to mixed drug toxicity (oxycodone, methadone, benzodiazepines, and trace HC). A fifth subject committed suicide 13 months after the study ended by mixed drug combination (hydromorphone, HC, dihydrocodeine, trazodone, and ethanol).

Abbreviations: C/T, conversion/titration; AE, adverse event; HC, hydrocodone.

overdose (two [0.5%], one HC-ER, one quetiapine), and dehydration (two [0.5%]). Two SAEs related to the study drug (one of mental impairment and one of lethargy, which were observed in a single subject) occurred during the C/T phase, and two SAEs related to the study drug (one mental impairment, one constipation) occurred during the maintenance phase. All drug-related SAEs resolved without intervention.

No clinically meaningful changes from baseline were observed in blood chemistry, hematology, or urinalysis for subjects who enrolled or did not enroll in the maintenance phase during the study.

One hundred percent drug accountability was required throughout the study, and 32 (5%) subjects during the C/T phase had drug accountability issues for HC-ER and/or rescue medication that suggested potential misuse or diversion. Twenty of these subjects were discontinued from the study; the remaining 12 subjects were determined to have plausible reasons for missing medication and remained in the study. Thirty-four (8%) subjects in the maintenance phase

were suspected of drug misuse or diversions; among these, 15 subjects were discontinued from the study and the remaining 19 continued in the study.

Effectiveness

The mean (\pm SD) average pain score improved from 6.4 ± 1.8 to 3.1 ± 1.1 from screening to the start of the maintenance phase among the subjects ($n=424$) who entered the maintenance phase (Figure 3). Mean average pain scores remained stable throughout the maintenance phase with a mean of 4.0 ± 2.2 ($n=391$) at the end of the study or early termination (Figure 3). From the start of screening to the start of the maintenance phase, 84% of the subjects had $\geq 30\%$ improvement in average pain scores and 61% of the subjects had $\geq 50\%$ improvement. At the end of the study, 55% had $\geq 30\%$ improvement of average pain scores from the start of screening and 40% of subjects had $\geq 50\%$ improvement.

Functional improvements were observed for BPI, HADS, and ODI scores during the study. BPI scores showed

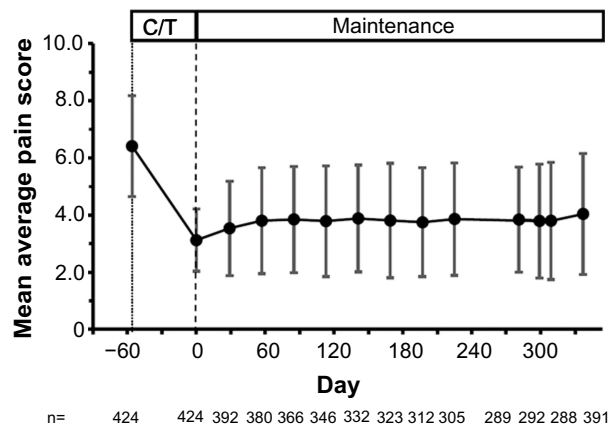


Figure 3 Mean average pain score from screening to the end of the study for patients who entered the maintenance phase.
Notes: The last point (day 337) also includes early termination. Error bars show standard deviation. Dotted and dashed vertical lines indicate screening and the start of the maintenance phase, respectively.
Abbreviation: C/T, conversion/titration.

functional improvements of approximately two points from screening to the start of the maintenance phase in all indices examined for patients who entered the maintenance phase, and this improvement was maintained over the 1-year study period. Patients who entered the maintenance phase showed small decreases (improvements) in HADS scores for both anxiety and depression (Table 3). Decreases in ODI scores indicated a shift from severe to moderate disability (Table 3) from screening to the start of the maintenance phase, and this improvement was maintained until the end of the study. In addition, SGAM scores indicated that 92% of subjects were at least moderately satisfied with their treatment at the end of the study.

Discussion

This study evaluated the long-term safety, tolerability, and effectiveness of HC-ER in patients with chronic pain who

Table 3 HADS and ODI scores of patients who entered the maintenance phase

| | Value at the start of the C/T phase | Change from the start of the C/T phase to the end of the Maintenance phase | |
|-----------------------------|-------------------------------------|--|-------------------|
| | | C/T phase | Maintenance phase |
| n | 424 | 423 | 392 |
| HADS total score, mean ± SD | | | |
| Anxiety | 6.68±2.95 | -0.89±2.80 | -0.85±3.69 |
| Depression | 5.54±3.31 | -1.28±3.24 | -0.71±3.86 |
| ODI, %, mean ± SD | | | |
| Disability | 41.2±14.9 | -10.2±13.4 | -6.8±14.5 |

Note: End of the maintenance phase includes early termination.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; ODI, Oswestry Disability Index; C/T, conversion/titration; SD, standard deviation.

were previously treated with an opioid, and found that HC-ER was generally well tolerated and had a safety profile consistent with other opioid medications. During the C/T phase, few patients withdrew due to AEs related to opioid withdrawal or uncontrolled pain, both surrogate markers for a suboptimal conversion from a prestudy opioid, suggesting that the conversion and titration from previous opioids were carried out appropriately.

No unexpected safety issues were identified. Constipation was the most common AE during the C/T and maintenance phases, similar to other opioids. AEs leading to discontinuations during the C/T phase included constipation, nausea, and headache, which are commonly seen with other opioids. In subjects who participated in the maintenance phase, the incidences of drug-related AEs were similar during the C/T and maintenance phases of the study. Similarly, the incidences of the opioid-related AEs constipation, nausea, and headache were similar in both phases of the study for these subjects, but the incidence of vomiting was four-fold higher in the maintenance phase (9.7%) than in the C/T phase (2.4%). Thus, no obvious trend for late-onset AEs for drug-related and opioid-related AEs was observed.

The observation that the incidence of opioid-related AEs did not increase during the maintenance phase compared with the C/T phase suggests that long-term treatment with HC-ER was not associated with “late-onset” opioid-related AEs. The rate of discontinuation due to AEs during the maintenance phase was low (8%), which suggests that subjects continued to tolerate the medication. Further, this study had a high completion rate in both the C/T (66%) and maintenance (67%) phases compared with trials of other long-term opioids,¹⁶ which reinforces that long-term treatment with HC-ER was well tolerated.

Four deaths occurred during the study; none was considered to be related to HC-ER. One of these subjects committed suicide by carbon monoxide poisoning and had a history of depression. Thirteen months after the study ended, another subject took their life by multiple drug toxicity (one of the five drugs was HC); hoarding of HC-ER may have been involved.

Average pain scores decreased from screening to the start of the maintenance phase then remained consistently lower by approximately two points throughout the maintenance phase, indicating that HC-ER maintained sufficient analgesia over the course of this long-term study. Improvements in effectiveness were also observed in functional activities, anxiety and depression, and disability assessments. Most patients were satisfied with their treatment at the end of the study.

The reduction in pain scores during the C/T phase suggests that these patients were not being adequately treated with opioids prior to enrolling in this study. Further evidence supporting this assumption was provided by the about two-fold increase in HC equivalent doses between screening and the end of the C/T period. The original insufficient dose may have been limited to reduce the possibility of toxicity associated with a nonopioid component. At the end of the C/T phase, patients who did not enter the maintenance phase had similar doses of HC to those who did enter. During the C/T phase, the total daily dose of rescue medication was similar between those who did or did not enter the maintenance phase. These values were also similar to the dose of rescue medication used during the maintenance phase.

This study design attempted to reflect typical clinical practice in the US. Subjects had a wide range of chronic pain types typically seen by clinicians, including osteoarthritis, low back pain, musculoskeletal pain, and neuropathic pain. Twenty-five (5.9%) subjects with fibromyalgia who had been receiving an opioid for chronic pain entered the maintenance phase, even though opioids are not recommended for patients with fibromyalgia.¹⁷ Individualized dosing was used throughout this study. Once the prespecified C/T algorithm was used to determine the starting dose of HC-ER, up- or down-titration of HC-ER was unlimited and at the investigator's discretion during the study. HC/APAP, a typical rescue medication, was permitted for breakthrough pain. Subjects were seen monthly during the maintenance phase, which also parallels the typical visit schedule used by pain clinics. Because of these elements, the study reflects usual clinical practice and strengthens the generalizability of study results.

Treatment of chronic pain needs regular, continuous dosing to maintain relief. The short half-life of HC-IR may limit its utility for treatment of chronic pain. Also, frequent dosing often results in poor medication adherence and may be associated with a higher incidence of AEs and dosing errors.¹⁸ ER formulations of opioids were developed to reduce the number of doses per day, improve pain control by reducing drug serum level variability, and enhance patient compliance with less frequent dosing.¹⁹ Here, we were able to show that HC-ER was able to achieve pain relief with dosing every 12 hours.

Chronic use of HC-IR combination products may put patients at higher risk for nonopioid toxicity. APAP is associated with liver failure at doses >4 g daily (more recent recommendations suggest that doses should not exceed 3.25 g/day).^{7,20} A recent systematic review by Blieden et al²⁰ showed that 63% of patients with acute liver failure

due to unintentional APAP toxicity were taking HC/APAP combination products at the time. Therefore, this single-entity formulation provides another option for patients who respond well to HC but require dosages that exceed the recommended daily dose of combination products. This formulation enables titration of HC without concern of inadvertent APAP overdose/toxicity. During the study, the daily use of rescue medication resulted in a mean daily dose of APAP of about 670 mg, which is well below the current recommended daily limit of 4,000 mg.²⁰

Some patients with chronic pain find benefit from one opioid, whereas others may be required to switch to another opioid (ie, "opioid rotation") if their current pain treatment becomes inadequate or if they experience intolerable AEs.^{21,22} This HC-ER formulation provides another option for opioid rotation.

As with all opioids, the risk of abuse exists. Therefore, the design of this study had a strict requirement of 100% accountability of opioid and rescue medication, higher than most opioid studies. The proportion of patients in both phases of this study who were unable to account for 100% of the medication was similar or lower compared with other opioid studies.^{23,24} However, the potential for diversion in this study may be underestimated because high-risk patients were excluded.

The primary objective of this study was to assess the long-term safety and tolerability of HC-ER, and the study was designed to approximate how this formulation would be used in clinical practice. The assessment of effectiveness, which was a secondary end point, is limited by the lack of a control group, and thus the contribution of a placebo effect to the overall response cannot be estimated. A limitation of this study was the lack of a control group and its open-label design. Additionally, the largest proportion of subjects entering the trial (37.5%) was converted from an HC/APAP product, which may have biased results in favor of HC-ER. Lack of statistical analysis was another limitation of this study.

The results of this long-term, open-label study of HC-ER demonstrated the safety, tolerability, and effectiveness of HC-ER treatment for 1 year. HC-ER delivers the same daily amount of HC as with HC-IR but uses fewer doses. HC-ER is a potential treatment option for patients with severe chronic pain who require daily, long-term opioid treatment and for whom alternative treatment options are inadequate. It also addresses the unmet medical need for patients with chronic pain who can tolerate HC but not APAP or ibuprofen. HC-ER may also be useful in opioid rotation.

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