# JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

**Meeting Date: February 14, 2018**

## CL-108 (HYDEXOR)

## (Hydrocodone/Acetaminophen/Promethazine)

## ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

# 1.0 EXECUTIVE SUMMARY

Most adults can relate to a debilitating experience of nausea and vomiting (resulting from motion sickness, food poisoning, migraine, morning sickness, or medication) for which they would do almost anything to relieve those symptoms, including taking precautions to prevent or avoid the experience altogether, if able. Unfortunately, many patients suffer these same burdensome symptoms of nausea and vomiting induced by anesthesia postoperatively (PONV), chemotherapy (CINV), and medical procedures and treatment, particularly opioid therapy. This is the basis for our engagement with the United States (US) Food and Drug Administration (FDA) and the acknowledgement of CL-108's novel indication for the short-term management of acute pain and opioid-induced nausea and vomiting (OINV) (Pre-IND Meeting 08Nov2007).

Nausea and vomiting are pharmacologic effects of immediate-release (IR) opioids, with approximately 40% of patients prescribed an opioid reporting nausea and approximately 20% reporting vomiting.[1-5] Opioid analgesics are often an effective and appropriate choice for short-term management of acute pain following surgery, trauma, or other acute medical conditions. Nevertheless, some patients and physicians are willing to give up degrees of pain relief to avoid OINV.[6-9] Thus, OINV can lead to inadequate pain management, resulting from nonadherence or discontinuation of therapy. OINV can also result in postsurgical complications such as aspirational pneumonia, bleeding, and wound dehiscence.[10-14] These complications can negatively affect patient recovery, clinical outcomes, healthcare costs, and productivity.[10,13-15] There is currently no approved or proven therapy to treat acute pain while preventing and reducing OINV.

Charleston Laboratories, Inc. (Charleston) is committed to improving the short-term management of acute pain while preventing and reducing the burdensome symptoms of nausea and vomiting. CL-108 (HYDEXOR™), a novel treatment with a novel indication, was specifically designed to provide effective short-term (generally less than 14 days) management of acute pain with optimized dosing and bioavailability of an antiemetic to prevent and reduce OINV. CL-108 combines IR hydrocodone (7.5 mg) and acetaminophen (325 mg) (similar to Norco® and Vicodin®) with a unique rapid-release formulation of low-dose oral promethazine (12.5 mg). For nausea and vomiting, the most common effective dose of Phenergan is 25 mg every 4- to 6-hours for a total daily dose of up to 150 mg.[16] The dose of promethazine in CL-108 is half the most commonly prescribed oral dose of Phenergan®.[17] This rapid-release formulation of promethazine in CL-108 provides greater early bioavailability of promethazine than commercial promethazine, which may contribute to the efficacy of CL-108 in preventing and reducing OINV.

The two objectives that drove the development of CL-108 were (1) to develop a safe and effective therapy for patients with acute pain who require an opioid and are at risk of OINV; and (2) to address the abuse, misuse, and diversion of opioids for acute pain management. Charleston recognizes the public health implications of opioids, specifically IR opioids, and is committed to the national movement to address the opioid abuse crisis. While the currently to-be-marketed formulation of CL-108 is not an abuse-deterrent formulation, Charleston, in order to address the major issues caused by IR opioids, will implement a comprehensive abuse mitigation program that incorporates different risk management activities intended to mitigate the abuse of CL-108.

Regulators, manufacturers, and the medical community need to implement a multifaceted approach to more thoroughly address the opioid abuse crisis. Charleston agrees with Scott Gottlieb, MD (Commissioner of the US FDA) and the position of the FDA regarding the need for new

strategies to address the crisis of opioid addiction through innovation in packaging, storage, and disposal. The CL-108 abuse mitigation program is designed to meet these expectations through labeling, packaging, and commercialization. The program intends to reduce the availability and quantity of CL-108 by limiting the dose and duration of use, and by putting mechanisms in place to facilitate the return of unused CL-108 tablets.

Unlike chronic pain, acute pain generally decreases as the underlying cause is addressed and subsides within three months, while acute pain requiring treatment with an opioid is usually much shorter.[18] Scully and colleagues found that the optimal length of opioid prescriptions lies between 4 to 15 days for common medical procedures.[19] When opioids for acute pain are necessary, treatment duration of one to two weeks should be satisfactory in most situations. The proposed labeling for CL-108 is for use of generally less than 14 days with a proposed dosing schedule of one tablet every 4- to 6-hours as needed, for a maximum daily dosage of six tablets. This is a departure from the current practice of IR hydrocodone prescribing, which is one to two tablets every 4- to 6-hours as needed. Patients can be instructed to take a total of up to 12 tablets per day (limited to 12 tablets based on acetaminophen maximum dose), often for durations longer than 14 days.[17]

In addition, CL-108 tablets will be available only in limited-duration 3-, 5-, and 7-day packaging, utilizing an F1/Child Resistant Container Closure System (carton) for securing blistered tablets. Charleston intends to support the label and packaging limitations with the introduction of a buy-back program to reduce the availability of unused CL-108 tablets and ensure proper disposal. The implementation of these abuse mitigation measures is designed to reduce patient and non-patient exposure to CL-108. Charleston will also implement appropriate education, distribution, monitoring, surveillance, and pharmacovigilance programs, and will incorporate the principles of the class-wide IR opioid Risk Evaluation and Mitigation Strategy (REMS) proposed by the FDA.

In discussion and with advice from the Agency for the development of CL-108 as a treatment for acute pain and OINV, Charleston's clinical program enrolled more than 1,300 patients and subjects and was more extensive than typical 505(b)(2) programs. Two randomized, double-blind, placebo- and active-controlled multiple-dose Phase 3 trials demonstrate that CL-108 met its treatment objectives of providing clinically meaningful benefits on both acute pain and OINV. There were no new safety findings in the CL-108 clinical development program and the CL-108 label will be consistent with the individual component reference listed drug (RLD) labels regarding safety, warnings, and precautions. Furthermore, in a human abuse liability (HAL) study conducted to evaluate the abuse potential of CL-108 in nondependent recreational drug users, no new safety signals or increased safety risks, and no increased risk of abuse (i.e., "drug liking," "high," or "take drug again"), were observed at supratherapeutic doses of CL-108. As with all opioids, the CL-108 label will carry the same black box warning regarding its potential for abuse, misuse, and diversion. There is currently no approved or proven therapy to treat acute pain while preventing and reducing OINV. The clinical safety and efficacy data presented for CL-108 and the Agency's previous safety findings on the RLDs support the use of CL-108 for the short-term management of acute pain requiring an opioid in patients at risk of OINV.

## 1.1 Proposed Indication, Dosage, and Intended Population

| | |
|---|---|
| Proposed indication | HYDEXOR is indicated for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV). HYDEXOR is indicated when alternative treatments for pain are inadequate. |
| Proposed dosage | For short-term (generally less than 14 days) management of acute pain, initiate treatment with CL-108 in a dosing range of one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 6 tablets. |
| Intended population | CL-108 is intended to displace IR opioids for short-term management of acute pain in adults (≥ 18 years of age) who are at risk of OINV. Use of CL-108 in the elderly should be considered with caution. It is not intended for pediatric use or for patients with significant respiratory depression, acute or severe bronchial asthma, known or suspected gastrointestinal (GI) obstruction, or known hypersensitivity to hydrocodone, acetaminophen, promethazine, or any other CL-108 component. CL-108 should not be used in conjunction with another opioid. |

## 1.2 Product Development Rationale

Many patients taking IR opioids experience OINV, which can limit the efficacy of pain management and lead to serious complications. OINV is common, with approximately 40% of patients reporting nausea and approximately 20% reporting vomiting in clinical studies.[1-5] In addition, OINV can complicate surgical recovery by delaying functional recovery, increasing the length of postoperative hospital stay and negatively affecting a patient's nutrition and healing.[13,14,20,21] There are no approved treatments to both manage acute pain and also prevent and reduce OINV. Current approaches to managing OINV can have unintended consequences such as rotating opioids (increasing the number of unused tablets) and higher dosing of antiemetics (increasing side effects). Moreover, treating OINV after these burdensome symptoms have emerged prolongs patient discomfort and significantly affects patient recovery, clinical outcomes, and healthcare costs.[10,13-15]

Equally important to the clinical challenges in acute pain management is the potential for abuse, misuse, and diversion, as shown by the high rates of unused opioids following prescription fill.[22] The most common source for prescription opioids that are abused, misused, or diverted is from a friend or family member.[23] Bicket and colleagues found that more than 67% of surgical patients reported having unused opioids.[24] Of all the opioid tablets obtained by surgical patients, up to 71% went unused. Data on opioid-naive surgery patients showed the optimal length of IR opioid prescriptions ranges from four to nine days for general surgery procedures, from 4 to 13 days for women's health procedures, and from 6 to 15 days for musculoskeletal procedures, suggesting that the optimal duration of IR opioid therapy for acute pain should not exceed one to two weeks.[19]

The lack of evidence to support the safe and effective coadministration of an opioid and an antiemetic, including currently approved labeling for hydrocodone/acetaminophen and promethazine that warns against coadministration of these central nervous system (CNS) depressants, inhibits a physician's ability to practice evidence-based medicine to manage acute pain and OINV. Moreover, incidence rates for OINV remain high and separate prescriptions could

result in increased safety risks, abuse, and medication errors; therefore, a need exists for a proven therapy to address acute pain while preventing and reducing OINV.

## 1.3 CL-108 Overview

CL-108 is a novel, bilayered tablet containing an IR opioid (7.5 mg hydrocodone) and a non-opioid pain reliever (325 mg acetaminophen) in combination with a unique formulation of a rapid-release, low-dose antiemetic (12.5 mg promethazine). CL-108 brings together one of the most commonly prescribed doses of hydrocodone, the most common dose of oral solid acetaminophen when combined with an opioid, and the lowest approved oral solid dose of promethazine. The novel combination in CL-108 demonstrated efficacy and a safety profile consistent with its individual ingredients with no new safety signals.

- Hydrocodone, a semisynthetic narcotic analgesic and antitussive with multiple actions, is qualitatively similar to codeine and, as with other narcotic (opiate) analgesics, blocks pain perception in the cerebral cortex by binding to mu-, kappa-, and delta-opioid receptors. Activation of these receptors in the CNS and GI tract by opioids triggers emetic pathways that lead to the vomiting center and subsequently causes nausea and vomiting.
- Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic agent. The analgesic mechanism of action of acetaminophen is not completely understood, but it appears to act through several centrally mediated mechanisms.
- Promethazine has a long history of safe and effective use, supported by multiple approved indications including as prevention and control of nausea and vomiting, as a sedative, as an adjunct to analgesics, and for motion sickness. Promethazine is the appropriate antiemetic choice for CL-108 because it addresses the underlying pathophysiology of OINV by inhibiting the histaminic, dopaminergic, and muscarinic receptors that stimulate the vomiting center. Different from commercially available promethazine, the rapid-release formulation of low-dose promethazine in CL-108 provides greater early bioavailability, which may contribute to the efficacy of CL-108 in preventing and reducing OINV. This unique formulation of promethazine in CL-108 differs from other promethazine formulations (solid dose, intravenous/intramuscular, syrup, see Section 8.4.1 for details).

## 1.4 CL-108 Development Program

In discussion and with advice from the Agency, Charleston designed a comprehensive CL-108 development program that surpassed the requirements of a typical 505(b)(2) program. The 505(b)(2) pathway allows bridging to safety and efficacy data for the currently marketed reference products approved by complete New Drug Applications (NDAs) based on pharmacokinetic (PK) assessments in relative bioavailability studies. The CL-108 development program comprised three PK studies, three Phase 3 studies, and one HAL study.

### 1.4.1 Nonclinical Overview

Given that all three active ingredients in the CL-108 formulation (hydrocodone, acetaminophen, and promethazine) are well characterized, additional nonclinical studies were not warranted. In support of the CL-108 505(b)(2) application, the Agency relied on previous findings of safety and effectiveness for the three active ingredients in CL-108 found in the RLDs: Vicoprofen tablet (containing hydrocodone 7.5 mg with ibuprofen 200 mg), Ultracet® tablet (containing

acetaminophen 325 mg with tramadol 37.5 mg), and Phenergan tablet (containing promethazine 12.5 mg). In addition, a literature review was conducted for each CL-108 ingredient in terms of pharmacology, drug metabolism, PK, and toxicology. Results from this review showed there are no new nonclinical findings that would affect the proposed therapeutic use of CL-108.

### 1.4.2 Clinical Overview

The clinical development program of CL-108 included seven clinical studies that evaluated the proposed to-be-marketed formulation of CL-108 (**Table A**). Overall, these studies enrolled more than 1,300 patients and subjects.

- Three Phase 1 relative bioavailability studies compared CL-108 to RLDs (or generic version; Study 004) or Norco (Studies 012 and 013) in healthy subjects.
- Two pivotal Phase 3 efficacy and safety studies compared CL-108 with Norco for the incidence of OINV and compared CL-108 with placebo for pain reduction in patients who underwent oral surgery (Study 002) or bunionectomy (Study 003).
- One actual-use Phase 3 study evaluated the safety and effectiveness of CL-108 in patients treating acute flares of osteoarthritis of the knee or hip (Study 006).
- One HAL (Phase 1) study evaluated the clinical abuse potential of CL-108 in nondependent recreational drug users (Study 007).

**Table A. Overview of Clinical Studies in CL-108 Development Program**

| Study Number | Purpose | Phase | Patient/Study Type | N |
|---|---|---|---|---|
| CLCT-004 | Relative bioavailability of CL-108 to RLDs (fasted, fed) | 1 | Healthy volunteers | 20 |
| CLCT-012 | Relative bioavailability of CL-108 to Norco (fasted) | 1 | Healthy volunteers | 32 |
| CLCT-013 | Relative bioavailability of CL-108 to Norco (fed) | 1 | Healthy volunteers | 32 |
| CLCT-002 | Evaluate safety and efficacy for intended treatment uses | 3 | Oral surgery pain model | 466 |
| CLCT-003 | | | Bunionectomy pain model | 552 |
| CLCT-006 | Evaluate safety in actual use | 3 | Acute osteoarthritis (flare) pain model | 179 |
| CLCT-007 | Evaluate abuse potential | 1 | Nondependent recreational drug users | 40 |

Source: Clinical Overview, Table 1.

#### 1.4.2.1 Clinical Pharmacokinetics

The PK profile of CL-108 was evaluated in three relative bioavailability studies (with standard bioequivalence, crossover designs) in healthy volunteers (Studies 004, 012, and 013).

**Study 004**

Study 004 was a randomized, open-label, four-way crossover study conducted in 20 healthy adult subjects to compare a single dose of CL-108 to a single dose of the following RLDs under fasted and fed conditions: Vicoprofen tablet (generic version [hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg]), Ultracet tablet (tramadol HCl 37.5 mg/acetaminophen 325 mg), and Phenergan tablet (generic version [promethazine HCl 12.5 mg]).

All three active ingredients in CL-108 demonstrated bioequivalence to the respective components in the RLDs, in both the presence and absence of food (**Figure A**). Data from this study provided the bridge required under the 505(b)(2) pathway and supports the scientific appropriateness of reliance on the Agency's previous findings of safety and efficacy for the RLDs (Vicoprofen, Ultracet, and Phenergan) to support marketing approval of CL-108.

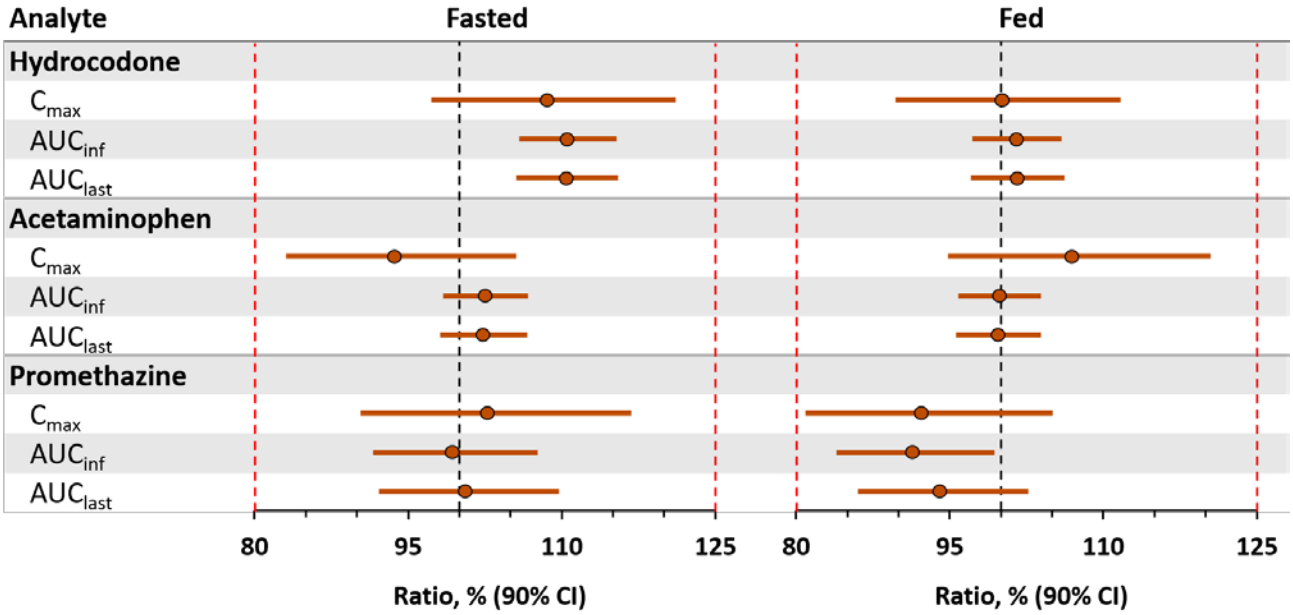


**Figure A. CL-108 is Bioequivalent to RLDs – Study 004**

Abbreviations: AUC, area under the concentration-time curve; $AUC_{inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; $C_{max}$, maximum concentration; CSR, clinical study report; RLD, reference listed drug.
Note: Bioequivalence was evaluated by comparing $C_{max}$ between CL-108 and the RLDs. This was repeated for AUC.
[a] Ratio (%) = Test/Ref x 100.
Source: 004 CSR, Tables 11.4.3.7, 11.4.3.8, 11.4.3.10, 11.4.3.11, 11.4.3.13, 11.4.3.14.

The unique rapid-release formulation of low-dose promethazine in CL-108 results in greater early bioavailability of promethazine than the commercial oral promethazine used as control. Mean promethazine concentration was greater in subjects receiving CL-108 (**Figure B**). Over the first hour after ingestion, exposure to promethazine was 59% higher with CL-108 versus the commercial product. This greater early bioavailability of the antiemetic may contribute to the efficacy of CL-108 in preventing and reducing OINV.

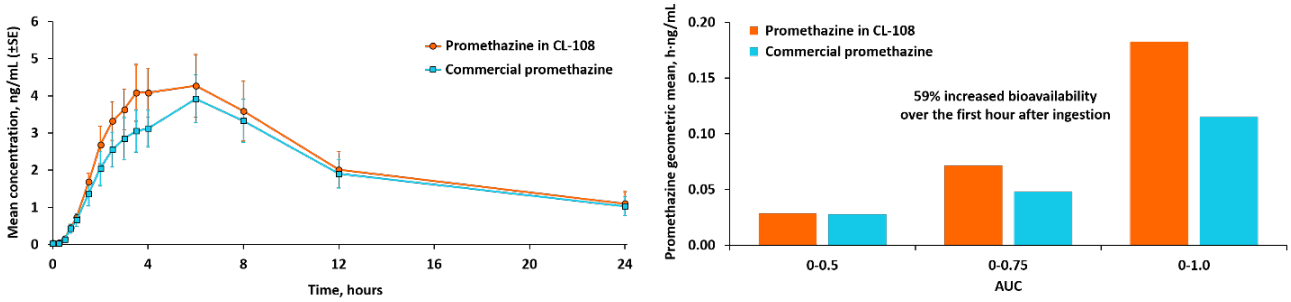


**Figure B. Relative Bioavailability of Promethazine in CL-108 (Fasted Conditions) – Study 004**

Abbreviations: AUC, area under the concentration-time curve; CSR, clinical study report; SE, standard error; USP, United States Pharmacopeia.
CL-108: 7.5 mg hydrocodone bitartrate, 325 mg acetaminophen, and 12.5 mg promethazine.
Reference Listed Drugs: Hydrocodone bitartrate and ibuprofen tablet, 7.5 mg/200 mg, promethazine hydrochloride (HCl) tablet, USP, 12.5 mg, and acetaminophen in Ultracet (37.5 mg tramadol HCl/325 mg acetaminophen) tablet.
Source: 004 CSR, Table 11.4.3.3 and Table 11.4.3.6.

### Studies 012 and 013

Studies 012 and 013 were single-dose, open-label, randomized, two-period, two-treatment, crossover studies in which 32 healthy subjects each were scheduled to receive a single dose of CL-108 in one period and a separate single dose of Norco in another period. Studies 012 and 013 compared the bioavailability of hydrocodone and acetaminophen in CL-108 with Norco under fasted (Study 012) and fed (Study 013) conditions. Norco was chosen as the comparator because it delivers the same dose of hydrocodone and acetaminophen per tablet as CL-108, and it was the comparator used in the pivotal Phase 3 trials (Studies 002 and 003). These PK studies were conducted at the request of the Agency to ensure that the exposure to hydrocodone from the two products is comparable in the safety and efficacy trials.

Results from these PK studies demonstrated that the hydrocodone and acetaminophen components of CL-108 are bioequivalent to Norco under both fed and fasted conditions (**Figure C**). Under fasted conditions in Study 012, time to maximum concentration ($T_{max}$) was longer with CL-108 compared with Norco (1.5 hours vs 1 hour). As a result, the abuse quotient (maximum concentration [$C_{max}$] divided by $T_{max}$) for CL-108 is lower than for Norco (12.9 vs 17.2) in healthy subjects.

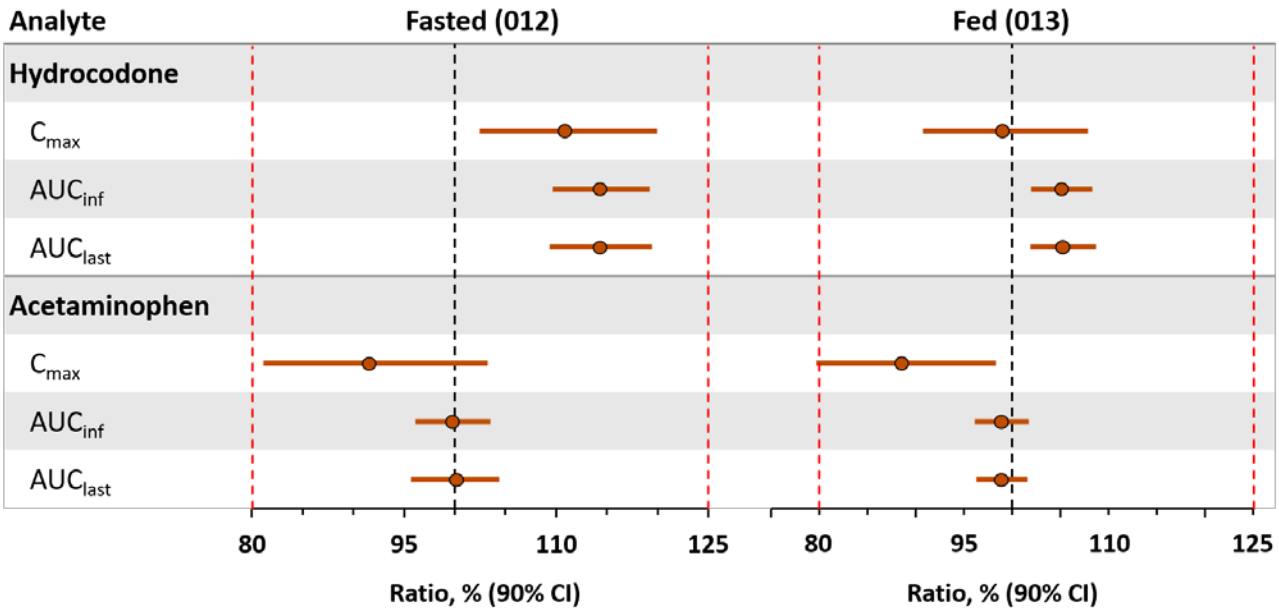


**Figure C. Hydrocodone/Acetaminophen in CL-108 Is Bioequivalent to Norco – Studies 012 and 013**

Abbreviations: AUC, area under the concentration-time curve; $AUC_{inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; $C_{max}$, maximum concentration; CSR, clinical study report; RLD, reference listed drug.
Note: Bioequivalence was evaluated by comparing $C_{max}$ between CL-108 and the RLDs. This was repeated for AUC.
[a] Ratio (%) = Test/Ref x 100.
Source: 012 and 013 CSRs, Tables 14.2.7 and 14.2.8.

### PK Conclusions

Overall, CL-108 was shown to be bioequivalent to hydrocodone, acetaminophen, and promethazine in the RLDs, and the safety and efficacy of each component can be bridged from the respective NDAs to CL-108. Hydrocodone in CL-108 was bioequivalent to Norco, thereby confirming that the clinical responses, particularly the reduced incidence of OINV observed with CL-108 in the pivotal trials (see Section 1.4.2.2 below), were not due to a difference in hydrocodone exposure. The unique rapid-release formulation of low-dose promethazine in CL-108 provides greater early bioavailability of promethazine than commercial promethazine, which may contribute to the efficacy of CL-108 in preventing and reducing OINV.

## 1.4.2.2 Clinical Efficacy

Two large, adequate, and well-controlled pivotal Phase 3 trials were designed to assess the efficacy of CL-108 in reducing acute pain and preventing and reducing OINV. Both were multicenter, randomized, double-blind, placebo- and active-controlled multiple-dose studies that used established, common acute pain models: oral surgery (Study 002) and bunionectomy (Study 003). Entry criteria were applied in both Phase 3 studies to enrich the study population with patients who were considered nausea prone. Patients with moderate-to-severe acute pain after surgery were randomized to receive CL-108, Norco, or placebo. In Study 002, dosing occurred every 4- to 6-hours, as needed for pain, over five days. In Study 003, patients were dosed five times per day for the first 48 hours and then every 4- to 6-hours as needed for pain over the remaining three days of the five-day study period. After the first dose, patients were observed in the clinic (for six hours in

Study 002 and for 48 hours in Study 003). Patients recorded hourly any vomiting and the intensity of pain and nausea throughout the 24-hour primary treatment evaluation period in Study 002 and throughout the 48-hour treatment evaluation period in Study 003. There were two co-primary endpoints in each study: (1) pain reduction by CL-108 compared with placebo; and (2) reduction in the incidence of OINV compared with Norco.

Study 002 was originally designed to enroll 810 patients. At an interim analysis after enrollment of 466 patients, the Independent Data Monitoring Committee reviewed the results and recommended stopping the trial based on their observations of (1) efficacy on both the analgesia and OINV co-primary endpoints; (2) no new safety findings; and (3) no difference in safety outcomes between patients treated with CL-108 and Norco.

A total of 466 patients were randomized 4:4:1 to CL-108, Norco, or placebo in Study 002, and 552 patients were randomized 5:5:1 to CL-108, Norco, or placebo in Study 003. In both studies, demographic and baseline characteristics were well balanced across the treatment groups.

### Co-Primary Endpoint Results

Both studies met their pre-specified co-primary endpoints (reduction in pain and OINV incidence).

Reduction in Pain

For Study 002, pain reduction was measured on a 0-3 categorical pain intensity scale and analyzed using the summed pain intensity differences from baseline over 24 hours ($SPID_{24}$). Patients in the CL-108 group had a significantly greater reduction in $SPID_{24}$ compared with placebo (16.2 vs 3.5; $p < 0.001$; **Figure D**). In Study 003, an analysis of summed pain intensity differences from baseline over 48 hours ($SPID_{48}$) was used to evaluate pain reduction measured on a 0-10 numerical pain intensity rating scale. This analysis demonstrated similarly significant results (118.4 vs 53.1; $p < 0.001$; **Figure D**).

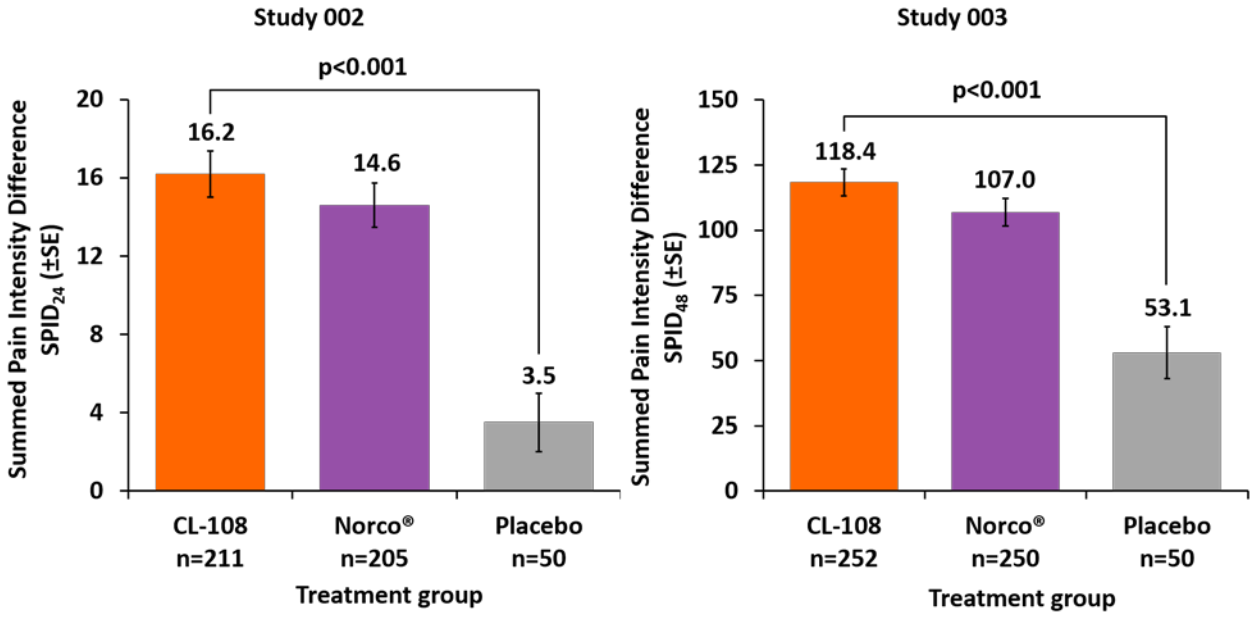


**Figure D. Analgesic Co-Primary Endpoint – Studies 002 and 003**

Abbreviations: CSR, clinical study report; SE, standard error; $SPID_x$, summed pain intensity difference over x hours.
Source: 002 CSR, Table 14.2.1.1 and 003 CSR, Figure 14.2.5.1.

Reduction in OINV Incidence

In Study 002, the presence of OINV over the primary 24-hour period was determined by a composite OINV endpoint with three components: (1) occurrence of any vomiting; (2) use of any supplemental (rescue) antiemetic; or (3) any report of greater than mild nausea. In absolute terms, the incidence of OINV was 22% lower in the CL-108 treatment group compared with the Norco group (36% vs 58%; $p < 0.001$; **Figure E**). This represents a 38% relative reduction in the risk of developing OINV with CL-108.

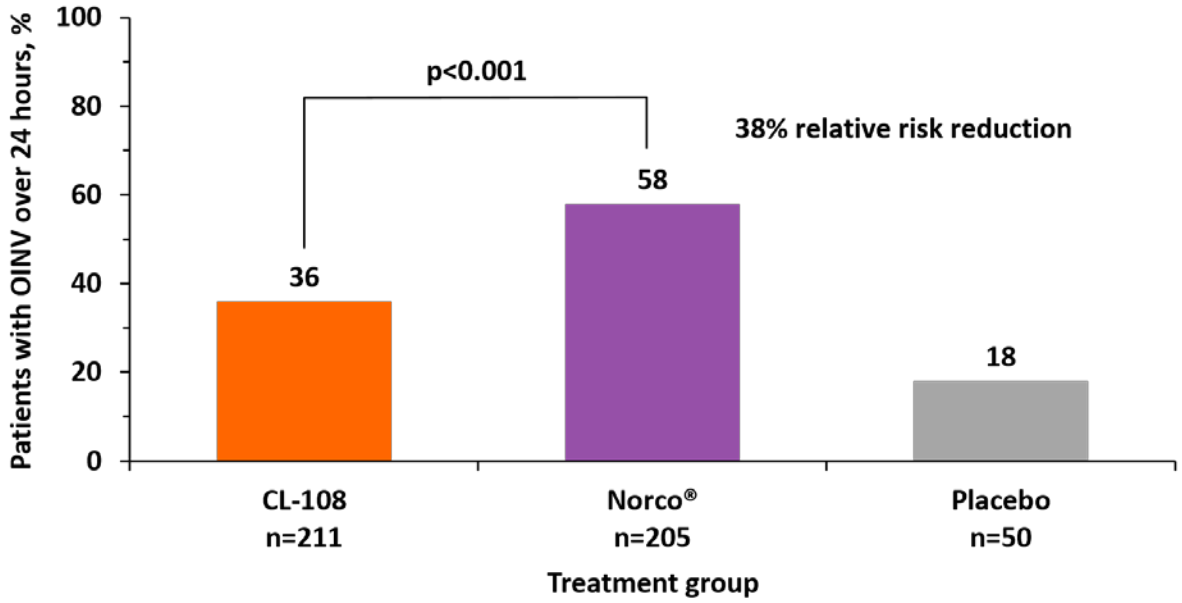


**Figure E. OINV Co-Primary Endpoint (Three Components) – Study 002**

Abbreviations: CSR, clinical study report; OINV, opioid-induced nausea and vomiting.
Source: 002 CSR, Table 14.2.1.1.

Based on feedback from the Agency regarding how to define OINV, a two-component definition of OINV based only on objective criteria was also assessed in Study 002: (1) occurrence of any vomiting; or (2) use of any rescue antiemetic. Using this two-component definition of OINV, the relative reduction in the risk of developing OINV in Study 002 was 64% (**Figure F**). This two-component definition also was used as the co-primary OINV endpoint in Study 003, which demonstrated a relative risk reduction of 74% (**Figure F**).

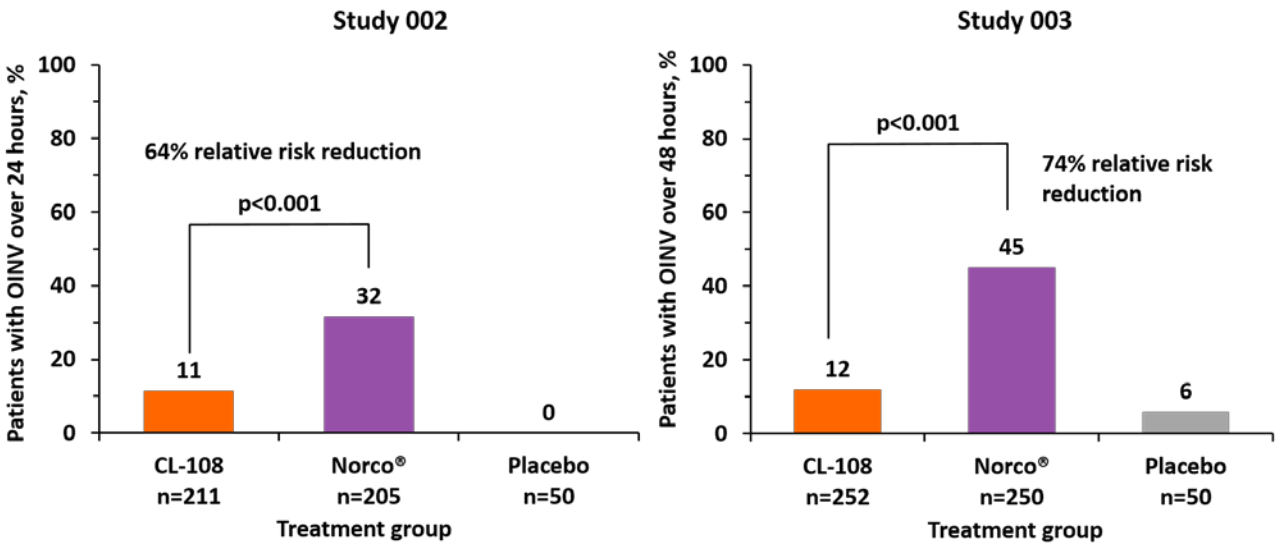


**Figure F. OINV Endpoint (Two Components) – Studies 002 and 003**

Abbreviations: CSR, clinical study report; OINV, opioid-induced nausea and vomiting; SE, standard error; $SPID_{24}$, summed pain intensity difference over 24 hours.
Source: 002 CSR, Table 14.2.3.7 and 003 CSR, Figure 14.2.5.2.

### Key Secondary Efficacy Endpoint Results

Consistent benefits of CL-108 were observed across key secondary and other pre-specified secondary endpoints of Studies 002 and 003, supporting the primary findings of pain reduction and reduced occurrence of OINV. In both studies, the intensity of nausea was significantly reduced by CL-108 compared with Norco. Significantly more patients using CL-108 reported a complete response (no nausea, vomiting, or use of antiemetic) than patients using Norco, presenting a strong indicator of OINV prevention in both studies. A significantly lower incidence of post-discharge nausea and vomiting and greater pain relief in patients with severe pain was also demonstrated in Study 003 by CL-108 compared with Norco. Refer to Section 6.0 for details of key secondary efficacy endpoint results.

### Efficacy Conclusions

Overall, CL-108 demonstrated consistent efficacy across two adequate and well-controlled pivotal trials. Both studies met their co-primary endpoints of providing significant pain reduction compared with placebo and significantly reducing the incidence of OINV compared with Norco. These studies also demonstrated consistent efficacy across key secondary and other secondary endpoints. Based on these results, CL-108 demonstrated efficacy in the short-term treatment of acute pain and prevention and reduction of OINV.

## 1.4.2.3 Clinical Effectiveness

Study 006 was an open-label, actual-use safety study in patients who experienced moderate-to-severe acute pain (flare) associated with osteoarthritis of the knee or hip that was inadequately managed (i.e., lack of efficacy or intolerance) with nonsteroidal anti-inflammatory drugs (NSAIDs). Patients took CL-108 as needed in the outpatient setting when they experienced a flare after discontinuing NSAID treatment. In addition to measuring clinical laboratory tests before and

after as-needed treatment with CL-108, this study also evaluated patient reports of the effectiveness (joint pain, stiffness, and function) and tolerability of CL-108. Patients documented all opioid-related symptoms and other adverse events (AEs) in a daily diary.

A total of 179 patients were enrolled. Results showed that 70.2% of patients reported improvement in joint pain and stiffness following treatment and > 20% improvement in specific activities of daily living, notably in the ability to walk one block (~31% improvement) and the ability to bathe or get dressed (~39% improvement; both $p < 0.0001$).

In addition, physicians rated CL-108 as "very good" (33.3%) or "excellent" (21.5%) for more than half of their patients. Compared with NSAID treatment at Screening, 94.8% of patients reported greater satisfaction with CL-108 treatment ($p < 0.0001$).

Overall, these findings under conditions of actual use support the consistent evidence of efficacy demonstrated in the pivotal Phase 3 trials.

#### 1.4.2.4 Clinical Safety

The safety profile of CL-108 is based primarily on data from Studies 002, 003, and 006, which enrolled nearly 1,200 patients.

**Exposure Across Studies 002, 003, and 006**

In the pooled pivotal studies (Study 002 and 003), the mean duration of exposure to CL-108 was 4.7 days, with a mean daily dose of 3.2 tablets. Exposure was similar in the Norco and placebo groups (mean duration of 4.5 and 4.1 days, respectively, and mean daily dose of 3.1 and 3.0 tablets, respectively). In Study 006, mean duration of exposure to CL-108 was 14.7 days with a mean daily dose of 2.0 tablets.

The observed exposure to CL-108 and Norco in the clinical studies, as well as data from the published literature,[19] recent state legislation and national guidance, and IMS prescription-level data were used to inform the most appropriate packaging quantities, which led to the 3-, 5-, and 7-day packaging (with F1/Child Resistant Container Closure System [carton] for securing blistered tablets). Refer to Section 10.2 for details.

**Studies 002 and 003**

A pooled safety analysis was conducted for the two randomized, pivotal trials. In these studies, 11 opioid-related symptoms were assessed. Two of these (nausea and vomiting) were directly measured on rating scales for the composite co-primary OINV efficacy endpoints. The other nine opioid-related side effects, including confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizzy, were captured through active surveillance using the Opioid Symptom Scale (OSS), adapted from the validated opioid-related Symptoms Distress Scale (SDS).[25] All other AEs were captured in a conventional, spontaneous, nondirective fashion. Due to differences in collection methods, AEs actively collected on the OSS are presented separately from other AEs. Each symptom was rated on a Likert scale, ranging from 0 (none) to 10 (severe). The OSS was administered at baseline and periodically following drug administration.

The incidence of opioid-related symptoms across the treatment groups for the pooled Studies 002 and 003 is shown in **Figure G**. Drowsiness was the most commonly reported of these symptoms across the two active treatment groups. Headache and dry mouth were also commonly reported

across all treatment groups, with high background incidences in the placebo group. Consistent with the inclusion of promethazine in CL-108, slightly higher rates of certain CNS events were observed with CL-108 compared with Norco. Most of these were assessed as mild or moderate and were without sequelae or consequence.

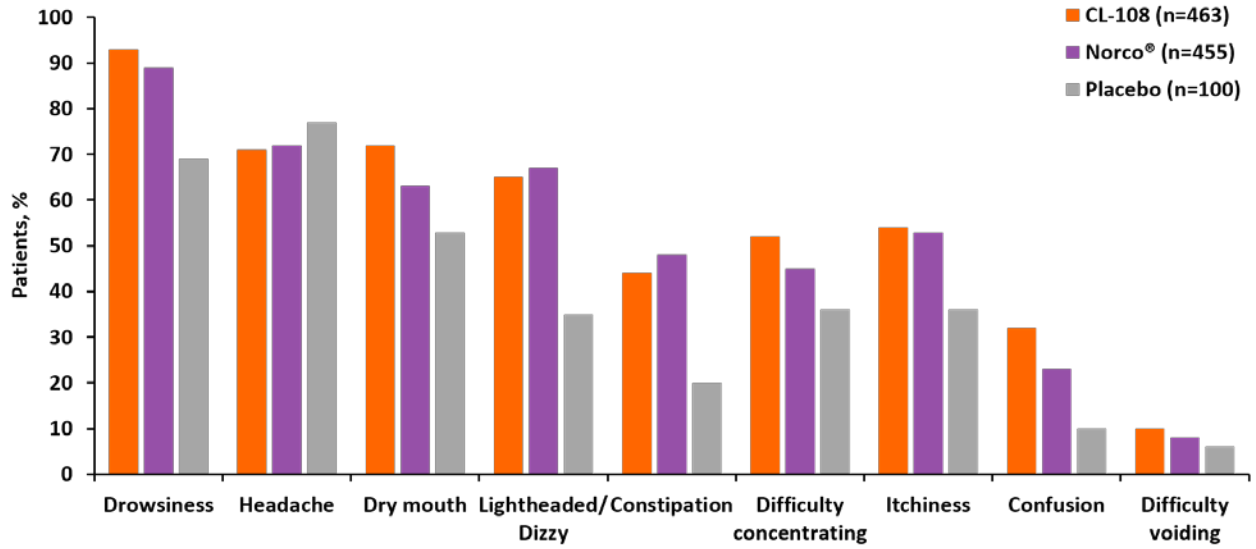


**Figure G. Other Opioid-Related Symptoms (OSS) – Pooled Studies 002 and 003**

Abbreviations: ISS, Integrated Summary of Safety; OSS, Opioid Symptom Scale.
Source: Appended ISS Table 2.3.15, Table 23.

Over the five-day treatment period, the mean severity of most opioid-related symptoms was rated as mild (i.e., ≤ 3 on the 11-point OSS) in the CL-108 and Norco groups. The exception was drowsiness, for which the mean severity was moderate. As would be expected following a surgical procedure, many patients reported pretreatment drowsiness, the incidence and severity of which improved over time in most cases with continued therapy; no patient discontinued study drug due to drowsiness. Given the fact that both hydrocodone and promethazine are known CNS depressants, drowsiness was expected, and a detailed analysis of drowsiness showed that it was dose related. However, there were no adverse sequelae for any patients reporting drowsiness.

Regarding spontaneously reported AEs (excluding nausea/vomiting and opioid-related symptoms), the incidence of events in the pooled studies was similar across the CL-108, Norco, and placebo treatment groups (26.3%, 26.2%, and 28.0%, respectively). There were two serious AEs (SAEs): breast carcinoma (CL-108 group) and cellulitis (Norco group), neither of which was assessed by the Investigator as related to study drug. Most AEs were reported as mild or moderate, and severe events were uncommon (range, 0.7% to 2.2%). No patient in the CL-108 group discontinued study drug due to an AE, and there were no deaths in either study.

Based on the known pharmacologic effects of the active ingredients in CL-108, there are several AEs of special interest (AESIs). In addition to nausea/vomiting and the nine opioid-related side effects, these include: syncope/presyncope, hypotension, pyrexia/increased body temperature, respiratory depression, dyspnea, seizure, and dyskinesia. The incidence of these events was low (≤ 3.0% across the treatment groups) or absent, and when there was a difference between CL-108 and Norco, the percentages were similar between CL-108 and placebo. Of note, no respiratory

depression was reported. None of the AESIs were serious; none resulted in dose reduction, study drug interruption, or discontinuation; and none resulted in clinically significant sequelae. All resolved without recurrence while on treatment.

### Study 006 (Actual-Use Safety Study)

The safety profile of CL-108 is further supported in an actual-use safety study (Study 006) in which patients took CL-108 as needed for acute pain every 4-to 6-hours over 14 days. Side effects, including nausea and vomiting, were reported voluntarily in diaries.

A total of 185 AEs that are typically considered opioid-related were reported by 81 patients (46%). Most of these opioid-related AEs were mild to moderate in severity. The most frequently reported events were drowsiness and lightheaded/dizziness, without adverse sequelae despite continued self-dosing (**Figure H**). The incidence of drowsiness and dizziness generally tended to decrease across the 14 days of treatment. Four patients reported nausea, including one patient who also reported vomiting, resulting in an OINV incidence of 2.2%.

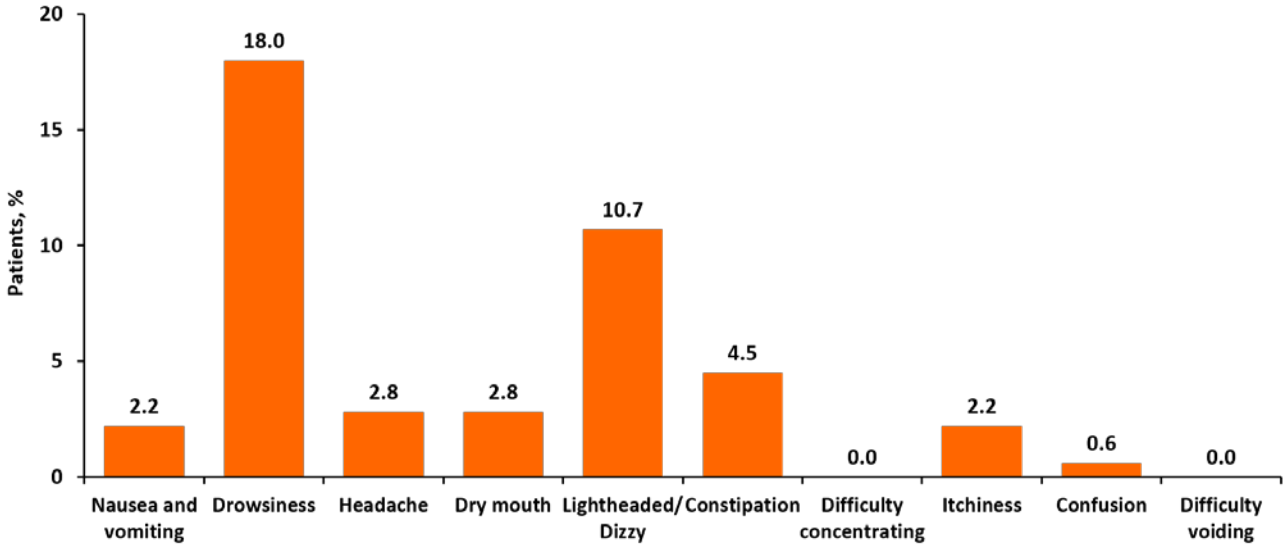


**Figure H. Frequency of Spontaneously Captured Opioid-Related Symptoms – Study 006**

Abbreviations: CSR, clinical study report.
Source: 006 CSR, In-Text Figure 13.

One patient in Study 006 experienced an SAE. This patient underwent an elective breast reconstruction procedure during the treatment period (previously scheduled but not revealed at enrollment) and developed a breast flap occlusion. Details of the surgery and postsurgical complication were reported only at the last study visit; the event was considered unrelated to study treatment and the patient recovered without sequelae.

### Safety Conclusions

Data from the two large, randomized, Phase 3 studies confirmed that the safety and tolerability of CL-108 is consistent with that of the individual components and their established profiles. Most events were mild to moderate in intensity and did not increase in frequency or severity as dosing continued, and no new specific safety signals were identified. None of the AESIs were serious or

resulted in discontinuation of study drug. The pivotal study safety observations are further supported by the actual-use safety study, a multi-dose study that allowed as-needed exposure over 14 days. Moreover, a thorough review of the FDA Adverse Event Reporting System (FAERS) from 1968 through the fourth quarter of 2016, examining nine predefined safety outcomes (respiratory depression, tardive dyskinesia, cognitive impairment, hypotension, syncope, torsade de pointes, reduction in seizure threshold, pyrexia and neuroleptic malignant syndrome, and somnolence) that could potentially be exacerbated by the combination of hydrocodone and promethazine, concluded that there are no new safety signals that are not addressed in the proposed label for CL-108.

#### 1.4.2.5 Human Abuse Liability

The addition of promethazine to hydrocodone may cause concerns regarding increased abuse potential. Promethazine itself can be abused, both alone and in combination with opioids, and concerns have been raised that promethazine may add to the abuse potential of hydrocodone. Therefore, a HAL study was conducted to evaluate whether the combination of promethazine and hydrocodone in CL-108 would have greater abuse potential.

**Study 007 (HAL Study)**

Study 007 was a randomized, double-blind, placebo-, and active-controlled, five-period crossover study in opioid-experienced, nondependent recreational drug users to determine whether the addition of promethazine might affect abuse potential. The study compared CL-108 versus placebo and CL-108 versus hydrocodone and acetaminophen alone. Comparisons were made at supratherapeutic doses (three and five times the recommended dose). The primary endpoint was the maximum effect ($E_{max}$) of drug liking on a bipolar visual analog scale (VAS) from 0 to 100, where a score of 50 was neither like nor dislike the effect at the moment. After Screening, subjects were given a naloxone challenge to ensure they were not physically dependent on opioids. After a 12-hour washout period, they received 30 mg hydrocodone with 1,300 mg acetaminophen to determine if they could tolerate the treatment and distinguish it from placebo. Subjects with a 15-point difference on drug liking were randomized to the Treatment Phase of the study where they received each of the five treatments in a random sequence. All study medications were over-encapsulated in identical capsules for double-blinding. Assessments were made over 24 hours with a minimum washout period of approximately 72 hours between each treatment.

A total of 40 subjects were enrolled in the HAL study. In discussions with the Agency, this sample size was determined to be adequate to assess a potential increase in drug liking. Results from this study demonstrated no evidence of increased drug liking with CL-108 compared with matched doses of hydrocodone/acetaminophen (**Figure I**), confirming that the inclusion of promethazine in CL-108 did not increase drug liking. Both supratherapeutic doses (three and five times the therapeutic dose) demonstrated similar effects and tolerability to matching doses of hydrocodone/acetaminophen and placebo. In addition, significant differences between CL-108 and the control in terms of “high,” “good drug effect,” “bad drug effect,” or “take drug again” were not observed.

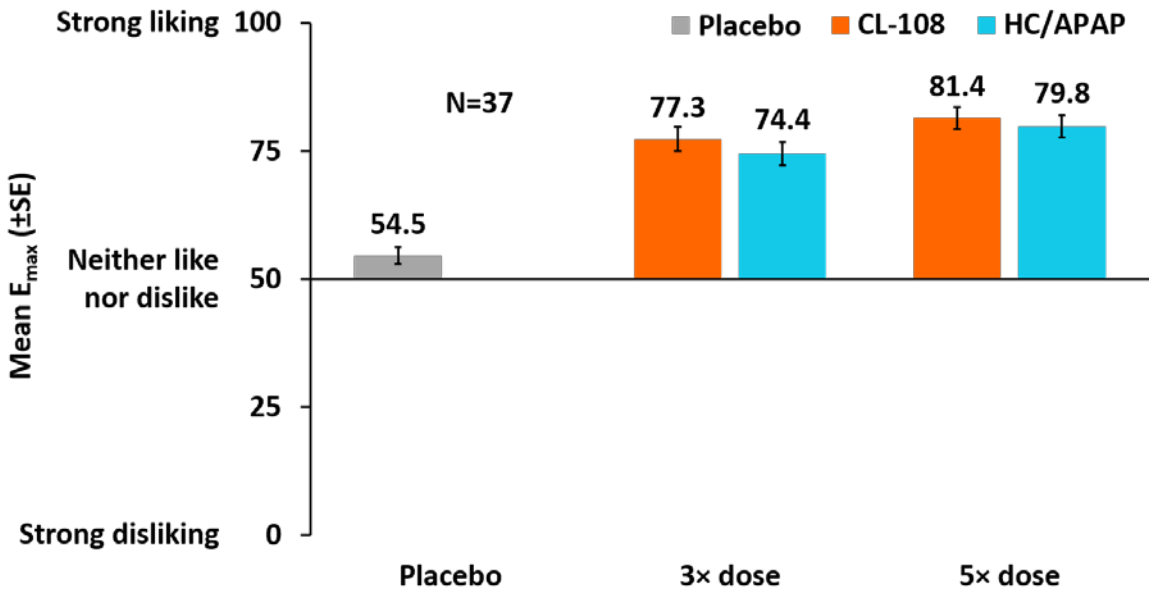


**Figure I. No Significant Increase in Drug Liking With CL-108 Versus Hydrocodone/Acetaminophen at Supratherapeutic Doses – Study 007**

Abbreviations: APAP, acetaminophen; CSR, clinical study report; $E_{max}$, maximum effect; HC, hydrocodone; SE, standard error.
p = 0.4737 CL-108 vs HC/APAP (5x dose), p = 0.2344 CL-108 vs HC/APAP (3x dose).
Source: 007 CSR, Tables 9 and 10.

In general, all treatments were well tolerated in this study with most treatment-emergent adverse events (TEAEs) being mild in severity and consistent with the known pharmacology of opioids (e.g., pruritus, euphoria) and promethazine (e.g., sedation). Overall, Study 007 showed that despite the presence of promethazine in CL-108, there was no increased risk of abuse, even at high supratherapeutic doses. Consistent with these findings, the abuse quotient for CL-108 in Study 012 is lower than for Norco (12.9 vs 17.2) in healthy subjects.

## 1.5 Risk Mitigation and Responsible Use

Although Charleston observed no increased risk of abuse with CL-108, we recognize the public health crisis caused by opioid abuse. Federal and state authorities across the nation are addressing this crisis, and we will participate in this movement. Charleston is committed to fostering responsible prescribing and safe use of CL-108 and will implement a comprehensive abuse mitigation program through labeling, packaging, and commercialization. This multifaceted approach is intended to help limit treatment duration and control dosing in an effort to reduce the number of unused CL-108 tablets available for potential abuse, misuse, and diversion.

Charleston's approach starts with labeling. Short-term use for acute pain (generally less than 14 days) has been defined and is stated both in the proposed label and patient medication guide. Second, Charleston has proposed a dosing schedule of one tablet every 4- to 6-hours as needed, for a maximum daily dosage of six tablets. This is a departure from the current practice of IR hydrocodone prescribing, which is one to two tablets every 4-to 6-hours as needed. Patients can be instructed to take a total of up to 12 tablets per day (limited to 12 tablets based on acetaminophen maximum dose), often for durations longer than 14 days.[17]

CL-108 will only be available in limited-duration (3-, 5-, and 7-day) packaging, utilizing an F1/Child Resistant Container Closure System (carton) for securing blistered tablets (**Figure J**).


**Figure J. Draft CL-108 3-, 5-, and 7-Day Packaging (F1/Child Resistant Container Closure System)**

In addition, Charleston intends to introduce a buy-back program in order to facilitate return of unused CL-108 tablets from patients for appropriate disposal of unused tablets that could be available for abuse, misuse, and diversion. These measures are designed to help change how CL-108 will be prescribed and used.

Finally, the CL-108 commercialization approach will involve implementation of appropriate education, distribution, monitoring, surveillance, and pharmacovigilance programs, and Charleston will collaborate with the Agency and other industry partners on the class-wide REMS for IR opioids.

## 1.6 Benefit-Risk Profile

Many patients taking IR opioids experience OINV, which can limit the efficacy of pain management and lead to serious complications. For example, OINV can negatively affect a patient's appetite and ability to eat,[20] leading to decreased nutrition, impaired wound healing, and decreased immune function, which can increase postoperative complications.[21] In addition, OINV can complicate surgical recovery by delaying functional recovery, increasing the length of postoperative hospital stay.[13,14] Currently, there are no approved treatments to address acute pain while preventing and reducing OINV, and current approaches to managing OINV with a separate prescription for an antiemetic can have unintended consequences. Moreover, treating OINV after burdensome symptoms have emerged prolongs patient discomfort and has significant effects on patient recovery, clinical outcomes, and healthcare costs.[10,13-15]

The efficacy and safety of CL-108 was demonstrated consistently across two pivotal Phase 3 studies and an actual-use Phase 3 safety study that enrolled nearly 1,200 patients. Both pivotal studies met their co-primary endpoints of providing significant pain reduction compared with placebo and significant reduction in the incidence of OINV compared with Norco. Efficacy was also observed across pre-specified key secondary and other pre-specified secondary endpoints. Enhanced analgesia was also observed, likely because of the effect of CL-108 on OINV. The clinical effectiveness findings from the actual-use study provided confirmation of the efficacy of CL-108 demonstrated in the pivotal Phase 3 trials when patients used CL-108 as needed for acute pain. Based on these robust efficacy results, if approved, CL-108 has the potential to improve acute pain management and patient recovery while reducing complications and associated costs.

The expected side effects, such as drowsiness, were mainly mild or moderate, diminished over the first two to three days while patients continued regular dosing, and did not result in discontinuations of study drug or serious complications. The safety and tolerability of CL-108 were consistent with the RLDs and their established PK and pharmacodynamic profiles, and no new safety signals were observed. Consequently, the CL-108 label will be consistent with the respective RLD labels regarding safety, warnings, and precautions about situations in which impaired mental ability can pose serious safety risks (e.g., driving and operating heavy machinery).

A significant need remains for a single approach to address both short-term management of acute pain when an opioid is required and the prevention and reduction of OINV. At the same time there is a need to foster new and more effective measures to address the opioid abuse crisis. Although the available epidemiologic evidence is limited regarding the prevalence of abuse, promethazine and other antihistamines can be abused in combination with opioids.

To this end, while no increased risk of drug liking or any secondary measure of abuse potential was observed at supratherapeutic doses of CL-108 compared to Norco in a HAL study, Charleston is committed to fostering responsible use of CL-108 and addressing the potential for abuse, misuse, and diversion. The CL-108 label will carry the same black box warning regarding its potential for abuse, misuse, and diversion, as with all opioids. CL-108 is intended for short-term use (generally less than 14 days) in the acute setting, and the limited-duration 3-, 5-, and 7-day packaging (with F1/Child Resistant Container Closure System) is designed to reduce the number of tablets dispensed. Charleston's intent is for these dosing and duration limitations to be supported through a buy-back program to facilitate patients' return of unused CL-108 tablets. Rather than expanding the use of IR opioids, CL-108 is intended to displace, not increase, existing IR opioid prescriptions among patients at risk of OINV.

The efficacy and safety data from the clinical development program combined with a comprehensive abuse mitigation program as well as the Agency's previous safety findings for the RLDs of CL-108, support a favorable benefit-risk assessment for CL-108.

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## LISTING OF IN-TEXT TABLES

## LISTING OF IN-TEXT FIGURES

# ABBREVIATIONS AND DEFINITIONS

| Abbreviation | Definition |
|---|---|
| λz | Elimination rate constant |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| APAP | Acetaminophen |
| API | Active pharmaceutical ingredient |
| APS | Arthritis Pain Scale |
| AUC | Area under the concentration-time curve |
| $AUC_{0-x}$ | Partial area under the concentration-time curve from time zero to x hours |
| $AUC_{Extrap(\%)}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{inf}$ | Area under the concentration-time curve from time zero extrapolated to infinity |
| $AUC_{last}$ | Area under the concentration-time curve from time zero to the time of the last quantifiable concentration |
| BLQ | Below limit of quantitation |
| BOCF | Baseline observation carried forward |
| CI | Confidence interval |
| CINV | Chemotherapy-induced nausea and vomiting |
| $C_{last}$ | Last quantifiable drug concentration |
| COPD | Chronic obstructive pulmonary disease |
| $C_{last}$ | Last quantifiable drug concentration |
| $C_{max}$ | Maximum concentration |
| CMC | Chemistry, Manufacturing, and Control |
| CNS | Central nervous system |
| CRL | Complete response letter |
| CSR | Clinical study report |
| CSS | Controlled Substance Staff |
| CTZ | Chemoreceptor trigger zone |
| CYP | Cytochrome P450 |
| DAAAP | Division of Anesthesia, Analgesia and Addiction Products |
| DDI | Drug-drug interaction |
| DGIEP | Division of Gastroenterology and Inborn Errors Products |
| $E_{max}$ | Maximum effect |
| EOP2 | End of Phase 2 |
| EPS | Extrapyramidal symptoms |
| FAERS | FDA Adverse Event Reporting System |
| FDA | Food and Drug Administration |
| GI | Gastrointestinal |
| HAL | Human abuse liability |
| HCl | Hydrochloride |
| IASP | International Association for the Study of Pain |
| IND | Investigational New Drug |
| IR | Immediate release |
| ISE | Integrated Summary of Efficacy |
| ISS | Integrated Summary of Safety |
| ITT | Intent-to-treat |
| LS | Least squares |
| MAOI | Monoamine oxidase inhibitor |

| Abbreviation | Definition |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| NA | Not applicable |
| NCS | Nausea Catastrophizing Scale |
| NDA | New Drug Application |
| NIS | Nausea Intensity Scale |
| NMS | Neuroleptic malignant syndrome |
| NNT | Number needed to treat |
| NPQ | Nausea Prone Questionnaire |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OINV | Opioid-induced nausea and vomiting |
| OSS | Opioid Symptom Scale |
| PDNV | Post-discharge nausea and vomiting |
| PGE | Physician's Global Evaluation |
| PI-CAT | Pain Intensity Categorical Scale |
| PI-NRS | Pain Intensity Numerical Rating Scale |
| PI-VAS | Pain Intensity Visual Analog Scale |
| PK | Pharmacokinetics |
| PMZ | Promethazine |
| PONV | Postoperative nausea and vomiting |
| PSO | Predefined safety outcome |
| PT | Preferred term |
| QDPI | Qualities of Dental Pain Index |
| QPI | Qualities of Pain Index |
| RADARS | Researched Abuse, Diversion and Addiction-Related Surveillance |
| REMS | Risk Evaluation and Mitigation Strategy |
| RHS | RAND 36-item health survey questionnaire |
| RLD | Reference listed drug |
| RVI | Retching/Vomiting Index |
| SAE | Serious adverse event |
| SATIS | Satisfaction Scale |
| SD | Standard deviation |
| SDS | Symptom Distress Scale |
| SMQ | standardized Medical Dictionary for Regulatory Activities (MedDRA) query |
| $SPID_x$ | Summed pain intensity differences over x hours |
| StomS | Stomach Scale |
| $t_{½}$ | Elimination half-life |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| $T_{last}$ | Time to last measurable concentration |
| $T_{max}$ | Time to maximum concentration |
| TOTPARx | Total pain relief over x hours |
| USP | United States Pharmacopeia |
| VA | Vestibular apparatus |
| VAS | Visual analog scale |
| VFS | Vomiting Frequency Scale |
| WNS | Worst Nausea Scale |
| WOCF | Worst observation carried forward |

# 2.0 PRODUCT DEVELOPMENT RATIONALE

## 2.1 Acute Pain Landscape

The International Association for the Study of Pain (IASP) defines acute pain as temporarily related to an injury or another identifiable cause such as surgery or an acute medical condition.[18] Unlike chronic pain, acute pain generally decreases as the underlying cause is addressed and subsides within three months. In cases where non-opioid therapies may be inadequate, immediate-release (IR) opioids are proven, effective analgesics with a known benefit-risk profile. Data on opioid-naive surgery patients showed the optimal length of opioid prescriptions range from four to nine days for general surgery procedures, 4 to 13 days for women's health procedures, and 6 to 15 days for musculoskeletal procedures,[19] suggesting that the optimal duration of opioid treatment for acute pain should be approximately one to two weeks.[19]

Charleston sees two major needs in the management of acute pain for patients requiring an opioid. First, there is a need for better options to manage acute pain, while preventing and reducing opioid-induced nausea and vomiting (OINV). Second, there is a need for innovative ways to address the opioid abuse crisis. Charleston intends to address these needs through the CL-108 drug development and abuse mitigation programs.

### 2.1.1 Opioid-Induced Nausea and Vomiting

Many patients requiring IR opioids suffer from nausea and vomiting, which can limit the efficacy of opioid medications and lead to serious complications. Studies suggest nausea is reported in approximately 40% of patients and vomiting is reported in approximately 20% of patients.[1-5] However, the cumulative incidence of OINV may be higher as several studies have demonstrated that most patients do not inform their healthcare provider when it occurs.[8,9,26]

Certain factors have been associated with an increased risk of nausea and vomiting in the postoperative setting, including a previous history of postoperative nausea and vomiting (PONV), motion sickness, and previous nausea and vomiting after taking an opioid-containing cough medication.[27] Certain demographic characteristics such as gender, nonsmoking status, and age are also associated with a higher risk for OINV.[27-29] Once it occurs, however, OINV is difficult to control, and there is currently no approved or proven therapy to treat acute pain while preventing and reducing OINV.

#### 2.1.1.1 Pathophysiology of OINV

Opioids cause nausea and vomiting by activating several areas that provide neural input to the vomiting center (Figure 1).[30] Activation of opioid receptors in the vestibular apparatus (VA), chemoreceptor trigger zone (CTZ), and gut cause nausea and vomiting signals to be relayed to the vomiting center. Recall of previous episodes of nausea and vomiting associated with opioid treatment are mediated by the cerebral cortex and thalamus.[30] Opioids activate opioid receptors across multiple organ systems; OINV and other side effects are pharmacologic effects of IR opioid treatment.[31,32]

- *CTZ*—The CTZ is located near the floor of the fourth ventricle on the dorsal surface of the medulla, largely outside the blood-brain barrier.[30,33] Toxins, metabolites, and other emetogenic compounds in the blood can activate the CTZ regardless of their blood-brain barrier

permeability. Opioids bind to and activate mu and delta receptors on the CTZ, which then release dopamine and serotonin on the vomiting center.[33]

- *Opioid stimulation of VA*—The precise mechanism by which opioids stimulate the vestibular system remains unknown.[30] Opioids are thought to enhance vestibular sensitivity by activation of mu-opioid receptors in the vestibular epithelium. After activation by opioids, vestibular fibers synapsing onto the vomiting center release histamine and acetylcholine and evoke its activation.
- *Opioid inhibition of GI function*—Opioids interfere with gastrointestinal (GI) motility and function via activation of mu-opioid receptors in the GI tract.[31,33-35] Resulting visceral stimuli then evoke a release of serotonin from the vagus nerve that activates the vomiting center.[33] Opioids may also inhibit the motility of smooth muscle in the esophagus, which may contribute to OINV.[35]
- *Brain-GI connection*—After receiving and integrating input from the brain and gut, the vomiting center sends signals to higher brain regions, causing the perception of nausea,[30,33,36] and may initiate a series of coordinated motor pathways to induce vomiting.[30]

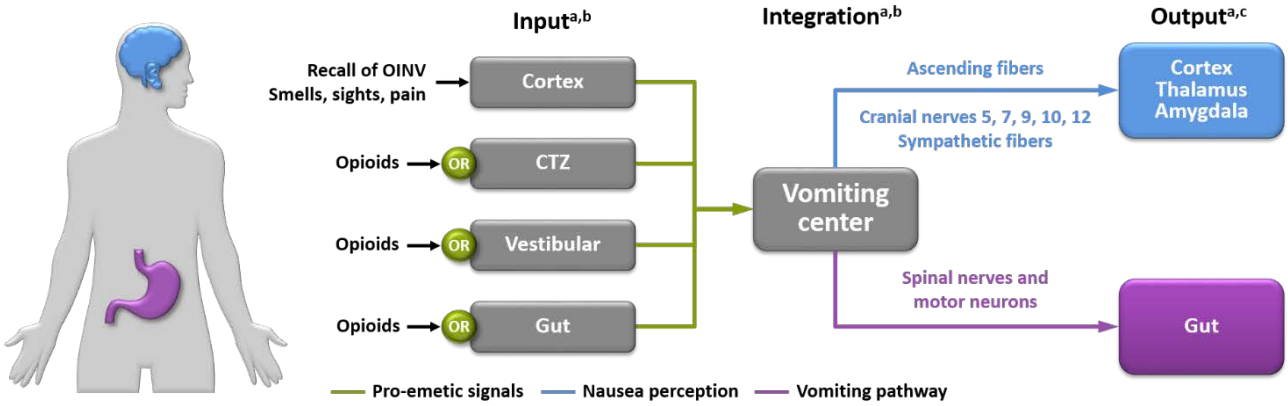


**Figure 1 Opioid-Induced Nausea and Vomiting Pathophysiology**

Abbreviations: CTZ, chemoreceptor trigger zone; GI, gastrointestinal; OR, opioid receptor.
[a] Coluzzi F, et al. *Curr Pharm Des.* 2012;18(37):6043-6052.[30]
[b] Porreca F, et al. *Pain Med.* 2009;10(4):654-662.[33]
[c] Horn CC, et al. *Eur J Pharmacol.* 2014;722:55-66.[36]

### 2.1.1.2 Burden of OINV

OINV is associated with significant patient-affected, clinical, and economic burdens. For the patient, OINV can lead to less effective pain management resulting in some patients taking their medications less frequently, or their medication not being fully ingested and absorbed. There can be additional unintended consequences such as rotating opioids (increasing unused tablets) and variable dosing of antiemetics (increasing side effects). OINV can also limit daily activities, affecting a patient's ability to concentrate, sleep, and move.[20] In fact, OINV can cause such significant discomfort that some patients would accept a lesser degree of pain relief from their opioid medication, or forego taking their pain medication altogether, to avoid or reduce nausea and vomiting.[6-9] Decreased pain relief can also be problematic because inadequate short-term pain management has been shown to be a potential factor in the progression to chronic pain.[37,38]

OINV also has important clinical implications. Following surgery, nausea and vomiting can delay functional recovery and increase a patient's hospital stay.[13,14] A retrospective study of orthopedic surgery patients found that vomiting was associated with an increase of 25% in the length of hospital stays.[13] In some cases, vomiting or retching is known to lead to surgical complications such as aspirational pneumonia, bleeding, and wound ruptures.[10]

There also are important economic implications from OINV. Marrett and colleagues found that in patients with acute pain initiating opioid therapy, those who experienced nausea and vomiting had increased use of healthcare services, including hospitalizations, and doctor's office/emergency room visits.[15] Among patients with a recent hospitalization, those who experienced nausea and vomiting had a 21% higher rate of 30-day rehospitalization, and their mean total healthcare costs were approximately $4,000 higher.

Reports have shown that both physicians and patients view reduction of opioid-related side effects, including OINV, as a key unmet need.[8,11] OINV may also affect pain management decisions. Patients and physicians indicated the occurrence of OINV as important when considering an opioid medication for pain management,[11] and OINV reduction and pain relief were rated as equally important attributes of an opioid medication by both patients and physicians.[8]

In summary, OINV has significant adverse effects on patient recovery, pain relief, clinical outcomes, and healthcare costs. These complications and the burden of OINV can lead to delayed recovery, increased healthcare resource utilization, and reduced productivity.[14,39] Therefore, preventing and reducing OINV are critical factors to improving acute pain management.

### 2.1.2 Opioid Abuse Crisis

The availability of unused medications directly contributes to the challenges society faces in addressing the opioid abuse crisis. Bicket and colleagues reviewed six studies involving surgical patients and found that more than 67% of all patients reported unused opioids and up to 29% reported opioid-induced adverse effects contributing to unused tablets.[24] This demonstrates that OINV can increase the potential for unused tablets available for abuse, misuse, or diversion.

Understanding the reasons for tablets going unused by patients is important for assessing the effect on the opioid abuse crisis; however, it is also important to recognize how a lack of disposal methods contributes to this crisis. To assess what happens to these leftover medications, Bicket and colleagues reviewed two studies and found that ≤ 9% employed United States (US) Food and Drug Administration (FDA)-recommended methods for disposal.[24]

Adverse effects of opioids result in inadequate management of acute pain, leading to unused tablets that are unlikely to be disposed of properly. More effective and appropriately controlled treatment options are critical to both improving the management of acute pain and helping address the opioid abuse crisis.

### 2.1.3 Conclusion

Short-term use of IR opioids is necessary for some patients with acute pain, but the nausea and vomiting induced by IR opioids present significant challenges to patient recovery, clinical outcomes, and economic effect. These adverse effects of OINV lead to inadequate short-term management of acute pain that contributes not only to the increased socioeconomic burden, but also to the number of unused tablets available for abuse, misuse, or diversion. Patients who require

an opioid would benefit from access to a single, proven therapy that not only reduces acute pain, but also prevents and reduces OINV.

# 3.0 CL-108 OVERVIEW

## 3.1 Drug Description

CL-108 is a novel, bilayered tablet containing an IR opioid (7.5 mg hydrocodone) and non-opioid pain reliever (325 mg acetaminophen) in combination with a unique formulation of a rapid-release, low-dose antiemetic (12.5 mg promethazine). The bilayered tablet has been specifically formulated to allow for the earlier and complete release of promethazine before that of hydrocodone and acetaminophen.

The chemical structure of each of the active ingredients in CL-108 is shown in Figure 2.

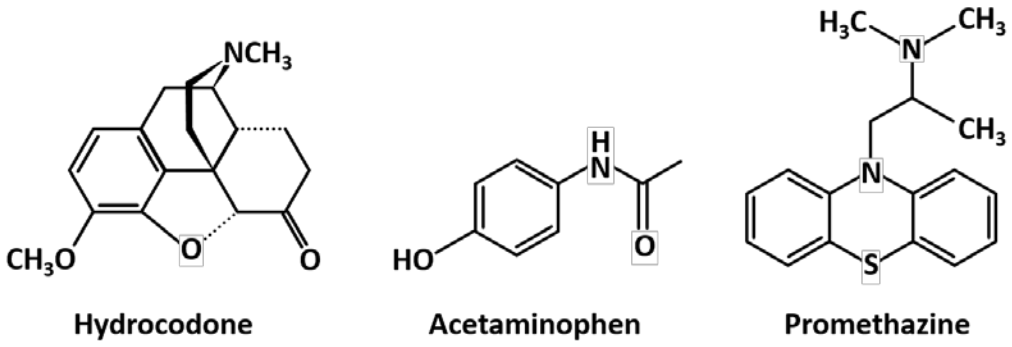


**Figure 2 Chemical Structures of Active Ingredients in CL-108**

## 3.2 Mechanism of Action

This section describes the mechanism of action of the individual components of CL-108 (hydrocodone, acetaminophen, and promethazine).

### 3.2.1 Hydrocodone

Although the precise mechanism of analgesia is unknown, specific central nervous system (CNS) opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the CNS and are thought to play a role in the analgesic effects of hydrocodone,[40-42] with most of its action on the mu-opioid receptor, and to a lesser extent the kappa- and delta-opioid receptors.[41,43,44] These receptors are G-protein–coupled receptors that inhibit cyclic adenosine monophosphate production and activate G-protein–mediated, inwardly rectifying potassium channels, the latter of which appears to be associated with the analgesic effect. In vitro experiments show that hydrocodone itself is a low potency agonist that is metabolized by cytochrome P450 (CYP)2D6 to hydromorphone, an active metabolite that is responsible for most of the drug's effects. Hydrocodone and hydromorphone are also metabolized by glucuronidation to either hydrocodone-3β-glucuronide and hydrocodone-6β-glucuronide or to hydromorphone-3β-glucuronide and hydromorphone-6β-glucuronide, respectively. The 3β metabolites of opioids are analgesically inactive, but the 6β metabolites may be as much as 100 times more potent at mu-opioid receptors than the parent compounds. Activation of the mu-, kappa-, and delta-opioid receptors in the CNS and GI tract triggers emetic pathways that lead to the vomiting center and subsequently cause nausea and vomiting.

### 3.2.2 Acetaminophen

Acetaminophen is a non-opiate, non-salicylate analgesic and antipyretic agent.[45] The analgesic mechanism of action of acetaminophen is not completely understood; however, it appears to act through a number of centrally mediated mechanisms, including inhibition of either methyl-D-aspartate or P-mediated nitric oxide synthesis.[46-49] It may also inhibit the release of prostaglandin E2 in the CNS.[47-49] Acetaminophen may also inhibit or modulate a pain mediator in the peripheral sites of injury and may selectively inhibit pain modulators in the spinal and supraspinal pathways of the CNS.[5,50] Other pathways in which acetaminophen may exert its analgesic effects include inhibiting lipoxygenase and cyclooxygenase, resulting in decreased prostaglandin and interleukin-1 synthesis in the hypothalamus, which are both involved in the transmission of pain. Acetaminophen can also increase the release of endogenous opioids in the periaqueductal grey matter, which inhibits pain pathways.[51-53]

### 3.2.3 Promethazine

Promethazine, a phenothiazine, acts as an antiemetic agent with dopamine, histamine (H1) and muscarinic receptor antagonist activity in the CNS.[54,55] Due to its H1-blocking ability, promethazine has antihistaminic action as well.[56] Like other H1 antagonists, promethazine competes with free histamine for binding at H1 receptor sites in the GI tract, uterus, large blood vessels, and bronchial muscle. Promethazine acts as an antagonist at both serotonergic (5-HT2A, 5-HT2C) and dopaminergic (D2) receptors.[57] The relief of nausea appears to be related to central anticholinergic actions and may implicate activity on the medullary CTZ.

Promethazine is approved for several indications, including the prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery; preoperative, postoperative, or obstetric sedation therapy adjunctive to meperidine or other analgesics for control of postoperative pain; sedation in both children and adults as well as relief of apprehension and production of light sleep from which the patient can be easily aroused; active and prophylactic treatment of motion sickness; and antiemetic therapy in postoperative patients. Promethazine is an appropriate antiemetic choice for CL-108 because it addresses the underlying pathophysiology of OINV (Figure 3) by inhibiting the dopaminergic, histaminic, and muscarinic receptors that stimulate the vomiting center. The average effective dose of Phenergan for the active therapy of nausea and vomiting is 25 mg, and according to the label, it may be dosed at 12.5 to 25 mg, repeated as necessary every 4- to 6-hours. As prescribed, a patient could take up to 150 mg in a 24-hour period. In comparison, even if six doses of CL-108 were taken in a 24-hour period, a patient would ingest a total of 75 mg promethazine, which is half the maximum total dose of commercial Phenergan when used alone. While, oral promethazine has a long history of safe and effective use, the unique rapid-release formulation of low-dose promethazine in CL-108 provides greater early bioavailability of promethazine than commercial products, which may contribute to the efficacy of CL-108 in preventing and reducing OINV.

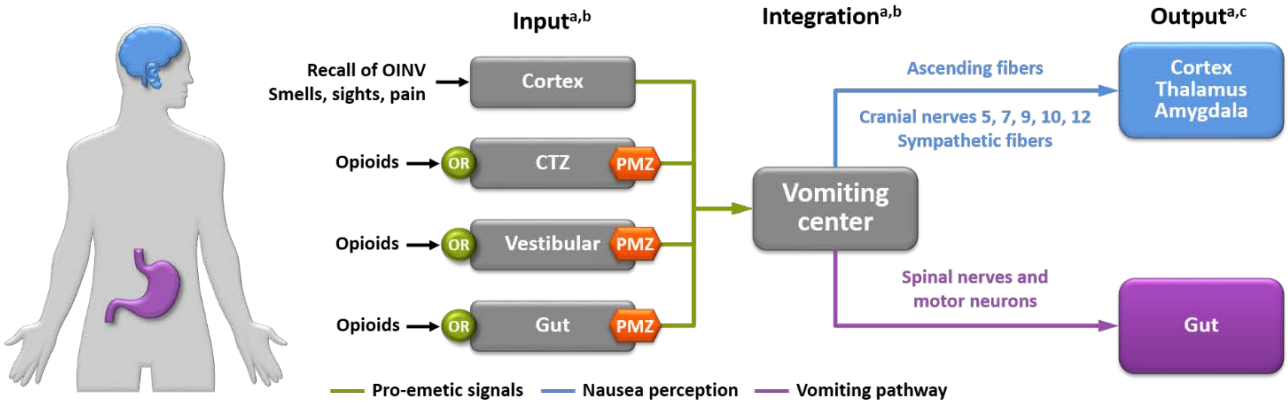


**Figure 3 Promethazine Addresses the Pathophysiology of OINV**

Abbreviations: CTZ, chemoreceptor trigger zone; GI, gastrointestinal; OINV, opioid-induced nausea and vomiting; OR, opioid receptor; PMZ, promethazine.
[a] Coluzzi F, et al. *Curr Pharm Des.* 2012;18(37):6043-6052.[30]
[b] Porreca F, et al. *Pain Med.* 2009;10(4):654-662.[33]
[c] Horn CC, et al. *Eur J Pharmacol.* 2014;722:55-66.[36]

## 3.3 Proposed Indication, Dosage, and Intended Population

### 3.3.1 Proposed Indication

HYDEXOR is indicated for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV). HYDEXOR is indicated when alternative treatments for pain are inadequate.

### 3.3.2 Dosage and Administration

For the short-term (generally less than 14 days) management of acute pain, initiate treatment with CL-108 in a dosing range of one tablet every four to six hours, as needed for pain. The total daily dosage should not exceed 6 tablets.

### 3.3.3 Intended Population

CL-108 is intended to displace IR opioids for short-term management of acute pain in adults (≥ 18 years of age) who are at risk of OINV. Use of CL-108 in the elderly should be considered with caution. It is not intended for pediatric use or in patients with significant respiratory depression, acute or severe bronchial asthma, known or suspected GI obstruction, or known hypersensitivity to hydrocodone, acetaminophen, promethazine, or any other CL-108 component. CL-108 should not be used in conjunction with another opioid.

# 4.0 CL-108 DEVELOPMENT PROGRAM

Charleston, in discussion with and with advice from FDA, designed a comprehensive CL-108 development program that surpassed the requirements of a typical 505(b)(2) program. The 505(b)(2) pathway allows bridging to safety and efficacy data for the currently marketed reference products approved by complete New Drug Applications (NDAs) based on pharmacokinetic (PK) assessments in relative bioavailability studies.

## 4.1 Regulatory History

As a 505(b)(2) application, the existing information related to active ingredients contained in reference listed drugs (RLDs) supported the safety and efficacy of CL-108. The FDA required demonstration of bioequivalence to the relevant or corresponding components in the RLDs, as well as conducting two Phase 3 studies to show safety and efficacy for the new indication.

In the Pre-Investigational New Drug (Pre-IND) meeting, it was agreed that the pivotal Phase 3 clinical trials would evaluate two co-primary endpoints: OINV and pain. At the End of Phase 2 (EOP2) meeting, the FDA accepted Norco® as an active comparator for OINV in the Phase 3 studies, although it could not be used as an RLD. At this EOP2 meeting, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requested that the primary endpoint for pain intensity from Study 002 (summed pain intensity differences over 24 hours [$SPID_{24}$]) be evaluated over 48 hours ($SPID_{48}$) under controlled dosing conditions in Study 003. Thus, pain was assessed using the $SPID_{48}$ as the co-primary analgesic endpoint in Study 003, based on fixed dosing for the first 48 hours (versus one tablet every 4- to 6-hours as needed for up to six doses in a 24-hour period in Study 002). Because of the existing information for the RLDs (as part of the 505[b][2] pathway), the FDA did not require extensive additional safety assessments.

Given that CL-108 is a new opioid-combination product, Charleston collaborated with the FDA and Controlled Substance Staff (CSS) to design a human abuse liability (HAL) study (Study 007) to evaluate whether CL-108, by reducing nausea and vomiting, could increase the abuse potential compared to other hydrocodone combination products (Pre-IND Meeting Minutes).

A Pre-NDA meeting confirmed that a multiple-dose PK study of CL-108 (to support a 505[b][2] pathway submission) was not necessary because the three active pharmaceutical ingredients (APIs) demonstrated similar PK profiles relative to the respective RLDs, in the presence or absence of food, in Study 004. The NDA for CL-108 was submitted on March 31, 2016.

On January 31, 2017, Charleston received a complete response letter (CRL) requesting additional data from two PK studies (Studies 012 and 013) and patent/administrative-related information. No deficiencies in Chemistry, Manufacturing, and Control (CMC) or Phase 3 data were included in the CRL. A Type A Meeting with the Division was held on June 19, 2017, to discuss the deficiencies outlined in the CRL and Charleston's plan to resubmit the NDA. The NDA was resubmitted on October 12, 2017.

## 4.2 Nonclinical Overview

Given that all three APIs in the CL-108 formulation (promethazine, hydrocodone, and acetaminophen) are well characterized, additional nonclinical studies were not required. Instead, the Agency's previous findings of safety and effectiveness for the three active ingredients in CL-108, found in the RLDs of Vicoprofen® (tablet containing hydrocodone 7.5 mg with ibuprofen

200 mg), Ultracet® (tablet containing acetaminophen 325 mg with tramadol 200 mg), and Phenergan (tablet containing promethazine 12.5 mg), were provided in support of the CL-108 505(b)(2) application. In addition, a literature review was conducted for each CL-108 ingredient in terms of pharmacology, drug metabolism, PK, and toxicology. Results from this review showed that there are no new nonclinical findings that would affect the proposed therapeutic use of CL-108.

## 4.3 Clinical Development Overview

The clinical development program of CL-108 included seven clinical studies that evaluated the proposed to-be-marketed formulation of CL-108 (Table 1). Overall, these studies enrolled more than 1,300 patients and subjects.

- Three Phase 1 relative bioavailability studies compared CL-108 to RLDs (or generic version; Study 004) or Norco (Studies 012 and 013) in healthy subjects.
- Two pivotal Phase 3 efficacy and safety studies compared CL-108 with Norco for the incidence of OINV and compared CL-108 with placebo for pain reduction in patients who underwent oral surgery (Study 002) or bunionectomy (Study 003).
- One supportive Phase 3 study evaluated the safety and effectiveness of CL-108 under conditions of actual use in patients with acute (flare) osteoarthritis pain of the knee or hip (Study 006).
- One Phase 1 study evaluated the clinical abuse potential of CL-108 in nondependent recreational drug users (Study 007).

**Table 1 Overview of Clinical Studies in CL-108 Development Program**

| Study Number | Purpose | Phase | Patient/Study Type | N |
|---|---|---|---|---|
| CLCT-004 | Relative bioavailability of CL-108 to RLDs (fasted, fed) | 1 | Healthy volunteers | 20 |
| CLCT-012 | Relative bioavailability of CL-108 to Norco (fasted) | 1 | Healthy volunteers | 32 |
| CLCT-013 | Relative bioavailability of CL-108 to Norco (fed) | 1 | Healthy volunteers | 32 |
| CLCT-002 | Evaluate safety and efficacy for intended treatment uses | 3 | Oral surgery pain model | 466 |
| CLCT-003 | | | Bunionectomy pain model | 552 |
| CLCT-006 | Evaluate safety in actual use | 3 | Acute osteoarthritis (flare) pain model | 179 |
| CLCT-007 | Evaluate abuse potential | 1 | Nondependent recreational drug users | 40 |

Source: Clinical Overview, Table 1.

# 5.0 CLINICAL PHARMACOLOGY

## 5.1 Pharmacokinetics

Consistent with 505(b)(2) requirements, a relative bioavailability study (Study 004) was conducted to bridge from CL-108 to each of the corresponding components in the RLDs, Vicoprofen (7.5 mg hydrocodone/200 mg ibuprofen; generic version), Ultracet (37.5 mg tramadol hydrochloride/325 mg acetaminophen), and Phenergan (12.5 mg promethazine; generic version). These drug products were selected for PK comparison of hydrocodone, acetaminophen, and promethazine, respectively, as each RLD had been approved with a full NDA based on clinical safety and efficacy data from pivotal trials. Additional bioequivalence studies (Studies 012 and 013) were conducted to compare the bioavailability of hydrocodone and acetaminophen in CL-108 to the same components in Norco. These three studies (Studies 004, 012, and 013) had standard bioequivalence and crossover designs. Results from these studies showed that CL-108 was bioequivalent to corresponding comparators of hydrocodone, acetaminophen, and promethazine. Additionally, the unique rapid-release formulation of low-dose promethazine in CL-108 leads to greater early bioavailability of promethazine than with commercial oral promethazine, which may increase the likelihood of preventing nausea and vomiting.

### 5.1.1 Bioavailability Study 004

#### 5.1.1.1 Overall Study Design and Methods

Study Design

Study 004 was a randomized, open-label, four-way crossover study conducted in 20 healthy adult subjects 19 to 76 years of age. The safety, tolerability, and PK of hydrocodone, acetaminophen, and promethazine in CL-108 versus the respective components in the RLDs (or generic versions), hydrocodone bitartrate 7.5 mg/ibuprofen 200-mg tablet, Ultracet tablet (tramadol hydrochloride [HCl] 37.5 mg/acetaminophen 325 mg), and promethazine tablet (promethazine HCl 12.5 mg) were evaluated under fasted and fed conditions. The RLD for the hydrocodone component was originally identified to be the Vicoprofen tablet (i.e., one of the listed drugs); however, Vicoprofen was not commercially available at the time of the study and was changed in Protocol Amendment 1 (dated October 24, 2014) to a generic hydrocodone/ibuprofen tablet (7.5 mg/200 mg). The FDA accepted use of the generic version of Vicoprofen. Similarly, a generic version of promethazine (promethazine HCl 12.5 mg) was used as a substitute for Phenergan, which had been discontinued and was not commercially available. Subjects were randomized to one of four treatment sequences (ABDC, BCAD, CDBA, DACB) and received one of the following treatments (single oral administration) during each study period:

- **Treatment A:** CL-108 (7.5 mg hydrocodone bitartrate/325 mg acetaminophen/12.5 mg promethazine) under fasted conditions
- **Treatment B:** CL-108 (7.5 mg hydrocodone bitartrate/325 mg acetaminophen/12.5 mg promethazine) under fed conditions
- **Treatment C:** Hydrocodone bitartrate 7.5 mg/ibuprofen 200-mg tablet + Ultracet tablet (tramadol HCl 37.5 mg/acetaminophen 325 mg) + promethazine HCl 12.5-mg tablet (all three tablets taken together) under fasted conditions

- **Treatment D:** Hydrocodone bitartrate 7.5 mg/ibuprofen 200-mg tablet + Ultracet tablet (tramadol HCl 37.5 mg/acetaminophen 325 mg) + promethazine HCl 12.5-mg tablet (all three tablets taken together) under fed conditions

Following a minimum 14-day washout period, each subject crossed over to receive an alternate treatment. This process was continued until each subject received the final alternate treatment during Period 4. Treatment under fasted conditions required at least 10 hours of overnight fasting. For treatment under fed conditions, following a minimum 10 hours of overnight fasting, subjects consumed an FDA standard high-calorie, high-fat meal 30 minutes prior to the administration of study drug.

Blood samples were collected at pre-dose (0 hours) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6, 8, 12, 24, and 48 hours post-dose.

Analyses

Data were analyzed by noncompartmental methods. In the PK analysis, concentrations below limit of quantitation (BLQ) were treated as zero from time zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing." Actual sample times were used for all PK and statistical analyses. The PK parameters that were determined included: maximum concentration ($C_{max}$), last quantifiable drug concentration ($C_{last}$), time to maximum concentration ($T_{max}$), time of the last measurable concentration ($T_{last}$), elimination rate constant, elimination half-life ($t_{½}$), area under the concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_{last}$), AUC from time zero extrapolated to infinity ($AUC_{inf}$), the percentage of $AUC_{inf}$ based on extrapolation ($AUC_{Extrap(\%)}$), and partial AUCs ($AUC_{0-0.25}$, $AUC_{0-0.05}$, $AUC_{0-0.75}$, $AUC_{0-1.0}$, $AUC_{0-1.5}$, $AUC_{0-2}$, and $AUC_{0-4}$).

PK parameters $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ were log-transformed before statistical analysis as recommended in the FDA guidance for statistical approaches to establishing bioequivalence and in the FDA guidance for bioavailability and bioequivalence studies of orally administered drug products. Bioequivalence was established if the 90% confidence intervals (CIs) of the geometric least squares (LS) mean ratios of $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ were within the 80% to 125% interval.

### 5.1.1.2 Study 004 Results

Patient Disposition

A total of 20 subjects participated in the study, of whom 19 subjects completed all four study periods. One subject voluntarily withdrew informed consent from the study prior to Period 3 check-in.

Demographic and Other Baseline Characteristics

The demographic characteristics of the 20 subjects are summarized in Table 2. Overall, most subjects were female (70.0%) and White (85.0%), and the mean age was 52.9 years.

**Table 2 Demographic Characteristics (Safety Population) – Study 004**

| Characteristic | Total (N = 20) | By Sequence | | | |
|---|---|---|---|---|---|
| | | ABDC (N = 5) | BCAD (N = 5) | CDBA (N = 5) | DACB (N = 5) |
| Age, years | | | | | |
| Mean | 52.85 | 54.60 | 46.80 | 55.60 | 54.40 |
| Standard deviation | 17.71 | 20.54 | 14.10 | 22.00 | 17.99 |
| Sex, n (%) | | | | | |
| Female | 14 (70.0) | 4 (80.0) | 3 (60.0) | 4 (80.0) | 3 (60.0) |
| Male | 6 (30.0) | 1 (20.0) | 2 (40.0) | 1 (20.0) | 2 (40.0) |
| Ethnicity, n (%) | | | | | |
| Hispanic or Latino | 11 (55.0) | 2 (40.0) | 2 (40.0) | 3 (60.0) | 4 (80.0) |
| Not Hispanic or Latino | 9 (45.0) | 3 (60.0) | 3 (60.0) | 2 (40.0) | 1 (20.0) |
| Race, n (%) | | | | | |
| White | 17 (85.0) | 5 (100) | 4 (80.0) | 5 (100) | 6 (60.0) |
| Black or African American | 2 (10.0) | 0 | 1 (20.0) | 0 | 1 (20.0) |
| American Indian or Alaska Native | 1 (5.0) | 0 | 0 | 0 | 1 (20.0) |

Abbreviations: CSR, clinical study report.
Source: 004 CSR, Table 14.1.2.

PK Results

Table 3 summarizes the main PK parameters of hydrocodone, acetaminophen, and promethazine following oral administration of a single tablet of CL-108 or the reference treatments, under fasted conditions. Overall, the results are consistent with those reported in the literature for IR formulations of hydrocodone, acetaminophen, and promethazine, when administered to healthy subjects and differences in dose are considered.

**Table 3 Summary of PK Parameters of Hydrocodone, Acetaminophen, and Promethazine Following Single Administration of One CL-108 Tablet or RLD Under Fasted Conditions – Study 004**

| PK Parameters[a] | CL-108 | | | Hydrocodone bitartrate 7.5 mg/ ibuprofen 200 mg | Ultracet | Promethazine HCL 12.5 mg |
|---|---|---|---|---|---|---|
| | Hydrocodone | APAP | Promethazine | Hydrocodone | APAP | Promethazine |
| $C_{max}$, ng/mL | 20.0 (27.42) | 4,710 (31.55) | 4.79 (78.24) | 18.4 (30.63) | 5,020 (33.06) | 4.35 (67.64) |
| $T_{max}$, h | 1.50 (0.50-3.00) | 0.75 (0.50-1.50) | 4.00 (2.50-6.00) | 1.00 (0.50-6.00) | 0.50 (0.25-2.00) | 5.02 (2.00-8.02) |
| $AUC_{inf}$, ng*h/mL | 150.2 (38.16) | 19,690 (29.38) | 96.92 (123.25) | 134.3 (35.88) | 19,160 (27.82) | 88.53 (113.25) |
| $t_{½}$, h | 4.93 (22.61) | 4.59 (23.18) | 17.49 (29.81) | 5.13 (22.94) | 4.52 (20.48) | 17.77 (31.33) |

Abbreviations: APAP, acetaminophen; $AUC_{inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $C_{max}$, maximum concentration; CSR, clinical study report; CV%, coefficient of variation; HCl, hydrochloride; PK, pharmacokinetics; RLD, reference listed drug; $t_{½}$, elimination half-life; $T_{max}$, time to maximum concentration.
[a] Mean (CV%) is shown for all PK parameters, except $T_{max}$ for which median (range) is presented.
Source: 004 CSR, Tables 14.2.13 through 14.2.24.

Under fasted and fed conditions, all three active ingredients in CL-108 demonstrated bioequivalence to the respective components in the RLDs (Figure 4). Data from this study provided

the bridge required under the 505(b)(2) pathway and supports the scientific appropriateness of reliance on the Agency's previous findings of safety and efficacy for the RLDs (Vicoprofen, Ultracet, and Phenergan) to support the marketing approval of CL-108.

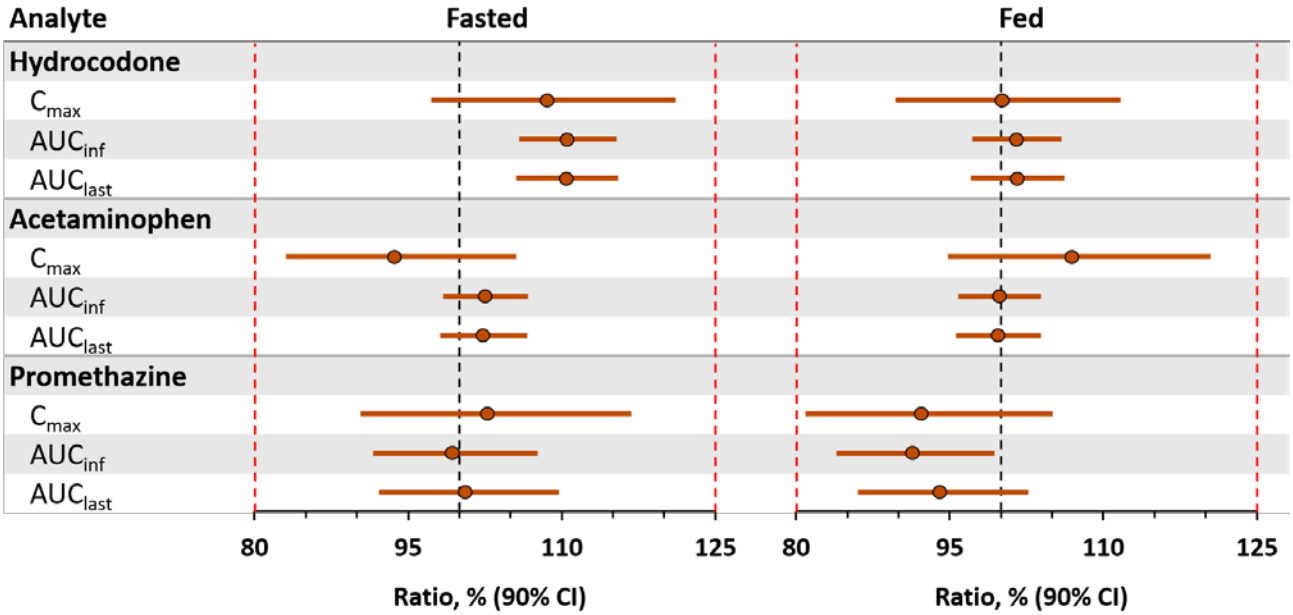


**Figure 4 CL-108 Is Bioequivalent to RLDs – Study 004**

Abbreviations: AUC, area under the concentration-time curve; $AUC_{inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; $C_{max}$, maximum concentration; CSR, clinical study report; RLD, reference listed drug.
Note: Bioequivalence was evaluated by comparing $C_{max}$ between CL-108 and the RLDs. This was repeated for AUC.
[a] Ratio (%) = Test/Ref x 100.
Source: 004 CSR, Tables 11.4.3.7, 11.4.3.8, 11.4.3.10, 11.4.3.11, 11.4.3.13, 11.4.3.14.

The unique rapid-release formulation of promethazine in CL-108 results in greater early bioavailability of promethazine than the commercial oral promethazine used as control (Figure 5).

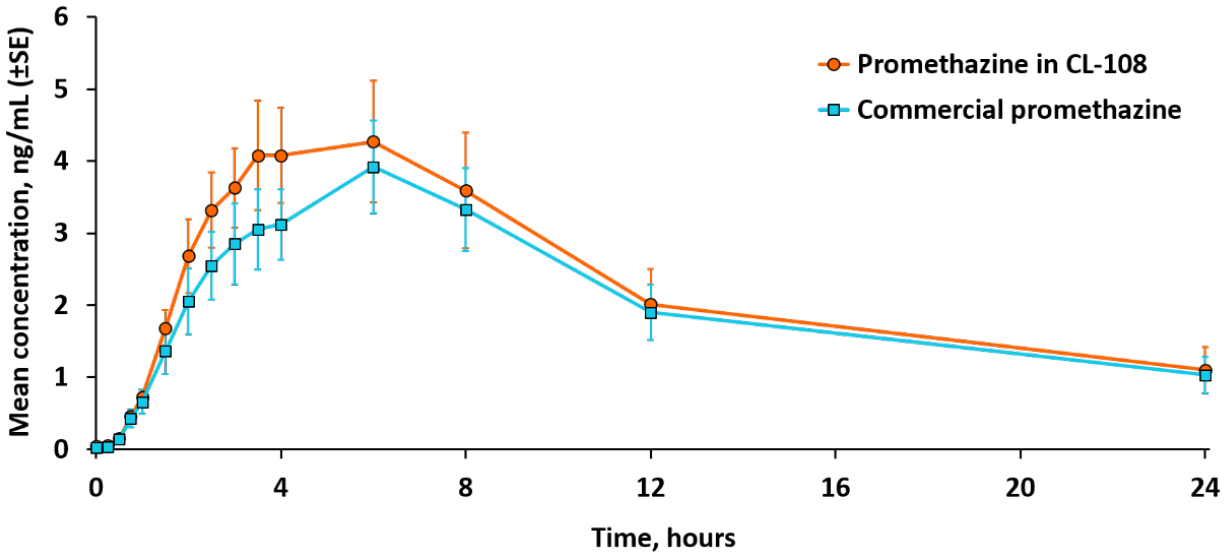


**Figure 5 Mean Promethazine Concentration (Fasted Conditions) – Study 004**

Abbreviations: CSR, clinical study report; SE, standard error; USP, United States Pharmacopeia.
Treatment A: 7.5 mg hydrocodone bitartrate, 325 mg acetaminophen, and 12.5 mg promethazine.
Treatment C: Hydrocodone bitartrate and ibuprofen tablet, 7.5 mg/200 mg, promethazine hydrochloride (HCl) tablet, USP, 12.5 mg, and acetaminophen in Ultracet (37.5 mg tramadol HCl/325 mg acetaminophen) tablet.
Source: 004 CSR, Table 11.4.3.3.

Over the first hour after ingestion, exposure to promethazine was 59% higher with CL-108 versus the commercial product (Figure 6). This greater early bioavailability of the antiemetic may contribute to the efficacy of CL-108 in preventing and reducing OINV.

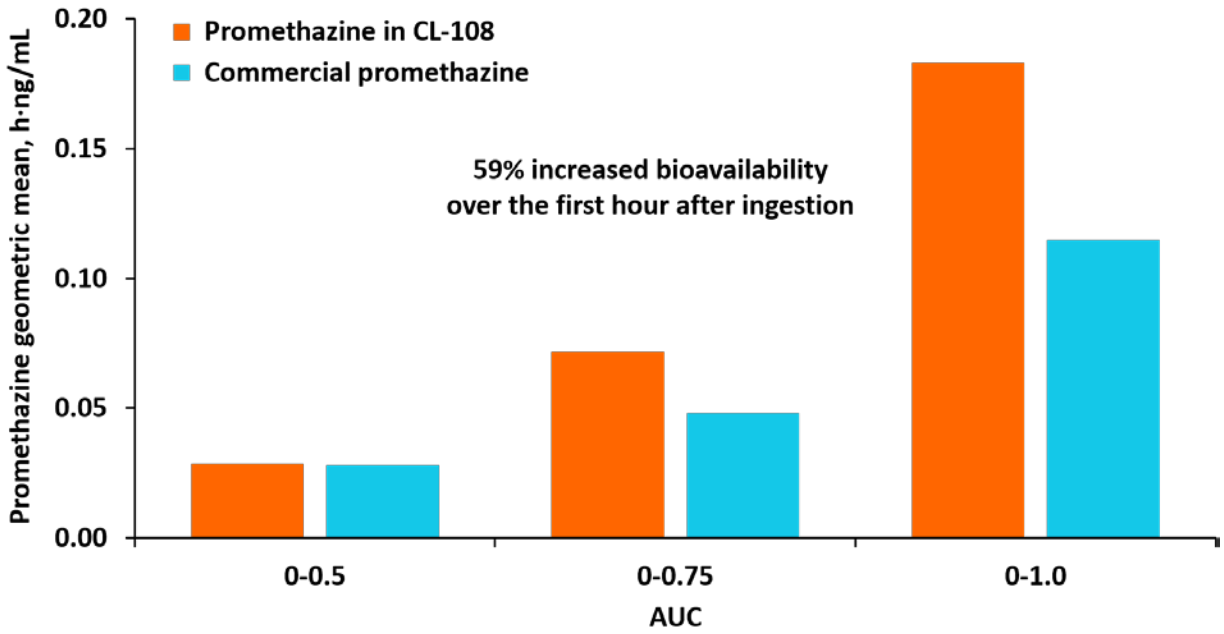


**Figure 6 Greater Early Bioavailability of Promethazine in CL-108 (Fasted Conditions) – Study 004**

Abbreviations: AUC, area under the concentration-time curve; CSR, clinical study report; USP, United States Pharmacopeia.
Treatment A: 7.5 mg hydrocodone bitartrate, 325 mg acetaminophen, and 12.5 mg promethazine.
Treatment C: Hydrocodone bitartrate and ibuprofen tablet, 7.5 mg/200 mg, promethazine hydrochloride (HCl) tablet, USP, 12.5 mg, and acetaminophen in Ultracet (37.5 mg tramadol HCl/325 mg acetaminophen) tablet.
Source: 004 CSR, Table 11.4.3.6.

### 5.1.2 Bioavailability Studies 012 and 013

#### 5.1.2.1 Overall Study Design and Methods

Study Design

Studies 012 and 013 were single-dose, open-label, randomized, two-period, two-treatment, crossover studies in which 32 healthy subjects each were scheduled to receive a single dose of CL-108 in one period and a separate single dose of Norco in another period. The objective of these studies was to compare the bioavailability of hydrocodone and acetaminophen in the to-be-marketed formulation of CL-108 with Norco under fasted (Study 012) and fed (Study 013) conditions. These studies were conducted per request of the Agency to ensure that the exposure to hydrocodone in CL-108 is comparable to the exposure of hydrocodone in Norco in patients randomized to CL-108 and Norco in the pivotal trials (Studies 002 and 003) examining the incidence of OINV. Subjects in Studies 012 and 013 were randomized to one of two treatment sequences (AB or BA) and received one of the following treatments (single oral administration) during each study period:

- **Treatment A:** CL-108 (7.5 mg hydrocodone bitartrate/325 mg acetaminophen/12.5 mg promethazine) under fasted (Study 012) or fed (Study 013) conditions
- **Treatment B:** Norco (7.5 mg hydrocodone bitartrate/325 mg acetaminophen) under fasted (Study 012) or fed (Study 013) conditions

Subjects in Study 012 fasted for at least 10 hours before each treatment and four hours after treatment. Standard meals were provided at approximately 4 and 10 hours after study drug administration.

Subjects in Study 013 fasted for at least 10 hours before each treatment followed by consumption of an FDA standard high-fat high-calorie breakfast meal 30 minutes before study drug administration.

Following a minimum seven-day washout period, each subject in Studies 012 and 013 crossed over to receive the alternate treatment. Blood samples were collected at pre-dose (0 hour) and at 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12.0, 24.0, and 48.0 hours post-dose.

Analyses

PK analysis methods used in Studies 012 and 013 were similar to those described above for Study 004 (see Section 5.1.1.1).

### 5.1.2.2 Studies 012 and 013 Results

Patient Disposition

In Study 012, a total of 32 subjects participated, of whom 31 subjects completed both study periods. One subject was discontinued early from the study due to deviation/noncompliance with the protocol at Period 2 check-in.

In Study 013, a total of 32 subjects participated, of whom 30 subjects completed both study periods. Two subjects discontinued early from the study due to deviation/noncompliance with the protocol at Period 2 check-in.

Demographic and Other Baseline Characteristics

Demographic and baseline characteristics of the populations in Studies 012 and 013 were similar (Table 4). Overall, more than half of the subjects were male, and most subjects were White and have never used tobacco. The mean age was approximately 38 years. The only difference between the two study populations was a higher incidence of Hispanic or Latino subjects in Study 013.

**Table 4 Demographic and Baseline Characteristics (Safety Population) – Studies 012 and 013**

| Characteristic | Study 012 (N = 32) | Study 013 (N = 32) |
|---|---|---|
| Age, years | | |
| Mean (SD) | 39.9 (13.76) | 36.9 (12.95) |
| Sex, n (%) | | |
| Female | 14 (43.8) | 14 (43.8) |
| Male | 18 (56.3) | 18 (56.3) |
| Race, n (%) | | |
| White | 21 (65.6) | 23 (71.9) |
| Black or African American | 9 (28.1) | 8 (25.0) |
| Multiple | 2 (6.3) | 1 (3.1) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 12 (37.5) | 20 (62.5) |

| Characteristic | Study 012 (N = 32) | Study 013 (N = 32) |
|---|---|---|
| Not Hispanic or Latino | 20 (62.5) | 12 (37.5) |
| Tobacco use, n (%) | | |
| Never | 27 (84.4) | 27 (84.4) |
| Past | 5 (15.6) | 5 (15.6) |

Abbreviations: CSR, clinical study report; SD, standard deviation.
Source: 012 and 013 CSRs, Table 14.1.2.

PK Results

Results from Studies 012 and 013 demonstrated that the hydrocodone/acetaminophen components of CL-108 are bioequivalent to those in Norco (the comparator drug used in the Phase 3 pain and OINV studies) under both fed and fasted conditions (Figure 7). Although the $C_{max}$ of hydrocodone was approximately 10% higher with CL-108 than with Norco under fasted conditions in Study 012, $T_{max}$ was longer with CL-108 compared with Norco (1.5 vs 1 hour) under fasted conditions. Therefore, the abuse quotient ($C_{max}$ divided by $T_{max}$) for CL-108 is lower than for Norco (12.9 vs 17.2) in healthy subjects. Also, the $C_{max}$ for acetaminophen under fed conditions (in Study 013) fell just below the 80% CI (at 79.69%), but there was no evidence that this 0.31% difference had any noticeable effect on pain reduction by CL-108. Together, results from these studies support the conclusion that the lower incidence of nausea and vomiting observed with CL-108 in the Phase 3 studies (described in Section 6.0 below) can be attributed to the presence of rapid-release, low-dose promethazine in CL-108.

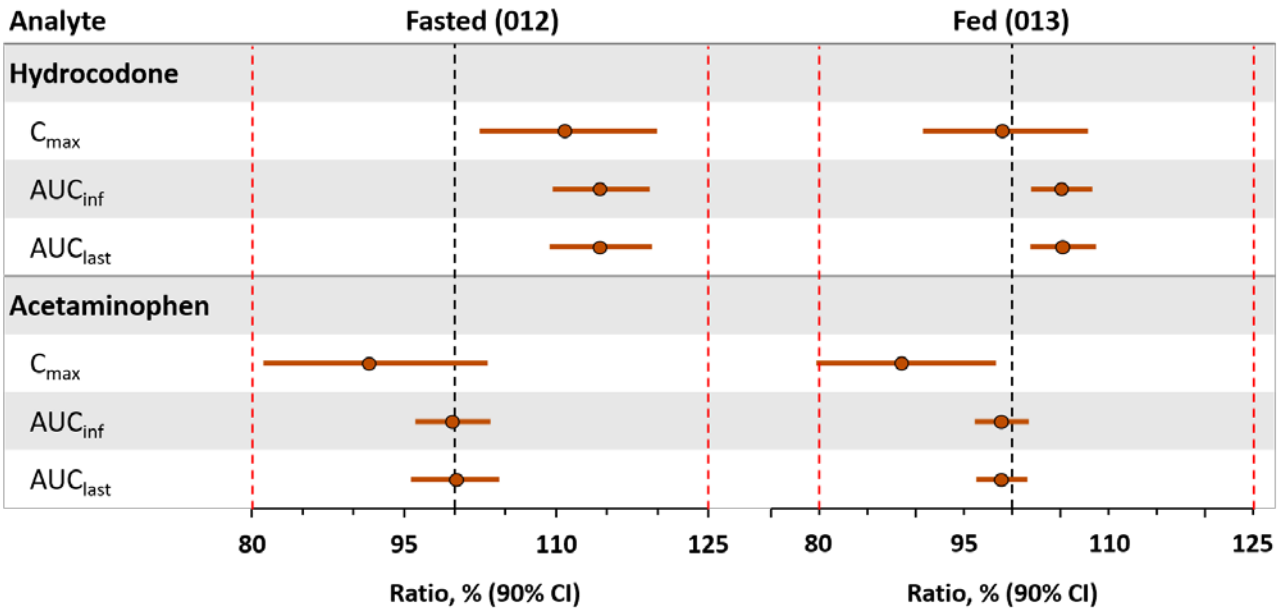


**Figure 7 Hydrocodone/Acetaminophen in CL-108 Is Bioequivalent to Norco – Studies 012 and 013**

Abbreviations: AUC, area under the concentration-time curve; $AUC_{inf}$, area under the concentration-time curve from time zero extrapolated to infinity; $AUC_{last}$, area under the concentration-time curve from time zero to the time of the last quantifiable concentration; CI, confidence interval; $C_{max}$, maximum concentration; CSR, clinical study report; RLD, reference listed drug.
Note: Bioequivalence was evaluated by comparing $C_{max}$ between CL-108 and the RLDs. This was repeated for AUC.
[a] Ratio (%) = Test/Ref x 100.
Source: 012 and 013 CSRs, Tables 14.2.7 and 14.2.8.

## 5.2 Food Effect

The bioequivalence criteria were met for hydrocodone, acetaminophen, and promethazine in both fed and fasted states. The presence of food modestly affected PK measures of the three components similarly in both CL-108 and the comparator drugs. Food reduced the $C_{max}$ of hydrocodone, acetaminophen, and promethazine in CL-108 by approximately 10.7%, 30.8%, and 8.6%, respectively; however, total exposure ($AUC_{last}$, $AUC_{inf}$) was similar (when administration under fasted and fed conditions was compared) for hydrocodone, slightly reduced for acetaminophen (approximately 5% to 6%), and slightly increased for promethazine (7% to 8.5%). Median $T_{max}$ for hydrocodone, acetaminophen, and promethazine were approximately 1.5, 2.0, and 2.0 hours longer, respectively, for CL-108 dosed under fed versus fasted conditions; a similar food effect was observed for the relevant RLD components. With similar drug exposures (under fasted and fed conditions), modest food effects on $T_{max}$ are not expected to be clinically relevant.

## 5.3 Drug-Drug Interactions

### 5.3.1 Pharmacokinetic Drug-Drug Interaction Potential for CL-108

There is no apparent PK drug-drug interaction (DDI) potential between the components of CL-108 (hydrocodone, acetaminophen, and promethazine). While both promethazine and hydrocodone are substrates of CYP2D6, promethazine is not expected to affect the PK characteristics of hydrocodone, nor is hydrocodone expected to affect the PK characteristics of promethazine. The

active metabolite of hydrocodone is hydromorphone, which is formed through CYP2D6 and represents only 3% of parent exposure. The coadministration of hydrocodone with paroxetine, a strong CYP2D6 inhibitor, did not affect systemic exposure to hydrocodone.[58] In addition, coadministration of hydrocodone with quinidine (100 mg single dose), a strong CYP2D6 inhibitor, has no effect on the PK of hydrocodone (Monograph for Hydrocodone, University of Washington DDI Database). Of note, there are or have been promethazine-opioid combination products available such as with codeine and meperidine. No PK DDIs have been reported in the literature for these marketed products. Therefore, it is unlikely that promethazine would affect the exposure of hydrocodone in CL-108.

### 5.3.2 Pharmacokinetic Drug-Drug Interaction Potential for RLDs

There is no apparent PK DDI potential for the components in the RLDs and those in CL-108.

The absorption, distribution, metabolism, and excretion properties of ibuprofen or tramadol do not suggest a potential PK DDI with hydrocodone, acetaminophen, or promethazine. Neither ibuprofen nor tramadol inhibit or induce CYP3A, a metabolic pathway for hydrocodone, nor do they inhibit or induce CYP2D6, a common metabolic pathway for hydrocodone and promethazine.[59-65] Also, neither ibuprofen nor tramadol affect UGT-glucuronyltransferases.

Based on a comparison of the PK of Vicoprofen to separately administered hydrocodone and ibuprofen as a three-way crossover study, there is no apparent effect of ibuprofen on the PK of hydrocodone (FDA Summary Basis of Approval, Vicoprofen). Based on the comparison of Ultracet to separately administered acetaminophen and tramadol, there is no apparent effect of tramadol on the PK of acetaminophen (FDA Summary Basis of Approval, Ultracet).

Results of the relative bioavailability studies further confirm a lack of PK DDI for any of the components of the RLDs with those of CL-108.

## 5.4 Clinical Pharmacology Conclusions

CL-108 was shown to be bioequivalent to hydrocodone, acetaminophen, and promethazine in the RLDs, and safety and efficacy can be bridged from the respective NDAs to CL-108 for each of the relevant components. Hydrocodone in CL-108 was bioequivalent to Norco, thereby confirming that the clinical responses, particularly the reduced incidence of OINV observed with CL-108 in the pivotal trials (see Section 6.0 below), were not due to a difference in hydrocodone exposure. The unique rapid-release low-dose formulation of promethazine in CL-108 provides greater early bioavailability of promethazine than commercial promethazine, which may contribute to the efficacy of CL-108 in preventing and reducing OINV.

# 6.0 CLINICAL EFFICACY

Efficacy results from two large, adequate and well-controlled pivotal Phase 3 studies using established pain models (oral surgery [Study 002] and bunionectomy [Study 003]) showed consistent, substantial, and clinically meaningful outcomes after treatment with CL-108. Both studies met their co-primary efficacy endpoints of reducing OINV compared with Norco and providing pain relief compared with placebo. These studies also demonstrated consistent efficacy across the pre-specified key secondary endpoints.

## 6.1 Study 002

### 6.1.1 Overall Study Design and Methods

#### 6.1.1.1 Study Design

Study 002 was a double-blind, randomized, multiple-dose, and placebo- and active-controlled multicenter study of CL-108 in patients with moderate-to-severe pain following surgical removal of impacted third molar teeth. Analgesia was determined by comparing CL-108 to placebo. An active control (Norco) was included to determine the antiemetic effects of CL-108.

The DAAAP recommended an enrichment procedure identifying patients who were likely or possibly nausea prone. This was determined by history (Nausea Prone Questionnaire [NPQ]) and, regardless of history, by observed response to an open-label opioid (hydrocodone challenge). Enrichment is a well-recognized and commonly used pre-randomization strategy of selecting a patient population to make a study more efficient and sensitive.[66]

In this study, up to 810 patients within two nausea prone stratifications (likely nausea prone and possibly nausea prone) were planned to be enrolled and randomized to one of three treatment groups: CL-108, Norco, or placebo at the ratio of 4:4:1 within each nausea prone stratum. However, at the initial interim analysis on 466 patients, an Independent Data Monitoring Committee reviewed the results and recommended stopping the trial based on their observations of (1) efficacy on both the analgesia and OINV co-primary endpoints, (2) no new safety findings, and (3) no difference in safety outcomes or physiologic measurements between patients treated with CL-108 and Norco.

After randomization, each patient received the first dose of investigational drug and remained at the clinic for efficacy and safety assessments until six hours after dosing. Patients were then discharged home. At home, patients self-dosed with one dose of the assigned study medication as needed for pain every 4- to 6-hours, for a maximum of six doses in a 24-hour period. Patients could take supplemental medications for pain and/or nausea/vomiting anytime according to label directions. Patients who used supplemental medication continued regularly scheduled evaluations of pain and nausea/vomiting and other side effects throughout the entire five-day dosing period. Approximately 5 (+2) days after surgery, patients returned to the clinic for final assessments and the end-of-study visit.

The design of Study 002 is illustrated in Figure 8.

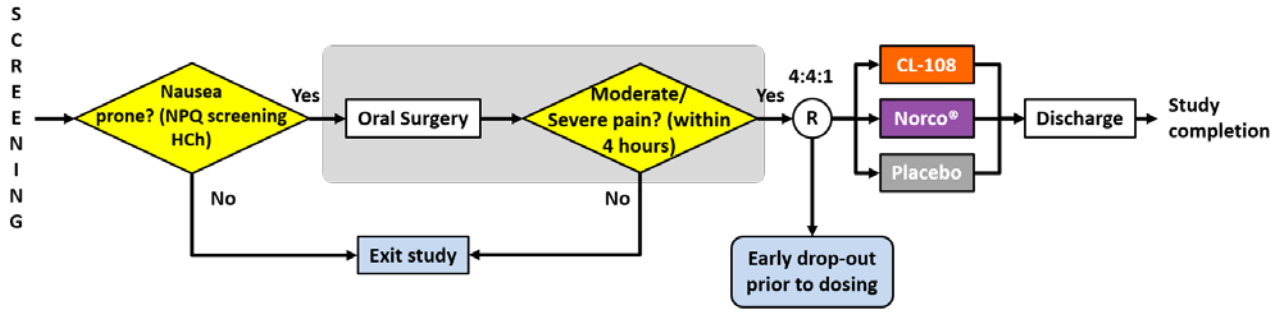


**Figure 8 Study 002 Design Schema**

Abbreviations: HCh, hydrocodone challenge; NPQ, Nausea Prone Questionnaire; R, randomization.

### 6.1.1.2 Key Eligibility Criteria

Key inclusion criteria were ≥ 18 years of age, nausea or vomiting after hydrocodone challenge and/or likely nausea prone or possibly nausea prone on the Screening NPQ, scheduled for surgical extraction of at least two impacted third molar teeth, pain rating of at least 50 mm on the Pain Intensity Visual Analog Scale (PI-VAS), and willing/able to complete patient diaries. Key exclusion criteria were presence of a serious medical condition, acute local infection at time of surgery, history of hypersensitivity to opioid drugs, promethazine, acetaminophens, nonsteroidal anti-inflammatory drugs (NSAIDs), use of any confounding/contraindicated products within 24 hours, use of investigational drug in last 30 days, and lack of adequate birth control/pregnancy or lactation.

### 6.1.1.3 Endpoints and Analyses

Primary Endpoint

The co-primary endpoints were OINV and analgesia. The co-primary endpoint of OINV was a composite index for the occurrence of OINV comparing CL-108 to Norco. This composite endpoint had three components: any vomiting, use of antiemetic medication, and moderate-to-severe nausea. OINV is a binary assessment of response/no response: a patient was considered a responder (i.e., a patient did not have OINV) if he or she experienced no vomiting and used no antiemetic medication at any time during the 24 hours post-randomization and experienced at most mild nausea (as documented by a rating of 1 to 3 on the 0 to 10 Nausea Intensity Scale [NIS]) during the initial 24 hours of treatment. A patient was considered a nonresponder (i.e., a patient had OINV) if he or she experienced moderate or severe nausea (as documented by NIS ratings of 4 to 6 or 7 to 10, respectively) or vomited (as documented by a rating of 1 to 3 on the 0 to 3 ordinal Vomiting Frequency Scale [VFS]) or received antiemetic medication at any time during the 24 hours post-randomization.

The co-primary analgesia endpoint was the time-weighted $SPID_{24}$, comparing CL-108 to placebo using results from a 4-point Pain Intensity Categorical Scale (PI-CAT) whereby patients rated their pain as none, mild, moderate, or severe. The endpoint was calculated at baseline, every 30 minutes until Hour 6, then every hour (while awake) until Hour 24 as follows:

- Each of the subsequent PI-CAT values was subtracted from baseline.

- Each difference was weighted by the elapsed time from the previous PI-CAT value to the current one.
- The weighted differences were summed to yield the $SPID_{24}$.

For patients who received supplemental medication for pain and/or nausea/vomiting during the six-hour period of the primary outcome measures, a baseline observation carried forward (BOCF) convention was used to impute the pain intensity and relief values and a worst observation carried forward (WOCF) convention was used to impute nausea/vomiting and other opioid symptoms (Opioid Symptom Scale [OSS]) values.

Key Secondary Endpoints

The key secondary endpoints comparing CL-108 to Norco included

- Summed intensity of nausea (on the NIS) over six hours
- Summed intensity of nausea (on the NIS) over 24 hours
- Frequency of vomiting (on VFS) over 24 hours
- Summed intensity of nausea (on the 0 to 10 Stomach Scale [StomS]) over six hours

Key Post-hoc Secondary Endpoint

The key post-hoc secondary endpoint was the incidence of vomiting or the use of antiemetic medication over the initial 24 hours. This two-component OINV endpoint was recommended by the Division of Gastroenterology and Inborn Errors Products (DGIEP).

### 6.1.2 Study 002 Results

#### 6.1.2.1 Patient Disposition

At the interim analysis, 466 patients were randomized, most of whom completed the study (Table 5). No pregnancies or deaths were reported during the study.

**Table 5 Patient Disposition (ITT/Safety Population) – Study 002**

| Parameter | CL-108 (N = 211) n (%) | Norco (N = 205) n (%) | Placebo (N = 50) n (%) |
|---|---|---|---|
| Treatment status | | | |
| Completed | 209 (99.1) | 203 (99.0) | 46 (92.0) |
| Discontinued | 2 (0.9) | 2 (1.0) | 4 (8.0) |
| Reasons for discontinuation | | | |
| Adverse event | 0 | 0 | 1 (2.0) |
| Lack of efficacy | 2 (0.9) | 0 | 2 (4.0) |
| Lost to follow-up | 0 | 1 (0.5) | 0 |
| Noncompliance with study drug | 0 | 0 | 0 |
| Withdrawal of consent | 0 | 0 | 1 (2.0) |
| Other | 0 | 1 (0.5) | 0 |

Abbreviations: ISE, Integrated Summary of Efficacy; ITT, intent-to-treat.
Source: ISE, Table 5 (Appended ISE Table 1.1.2).

#### 6.1.2.2 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics were generally well balanced across the randomized treatment groups (Table 6). Patients were predominantly female and White, and the mean age was approximately 22 years. Most patients had never used tobacco.

In each of the treatment groups, approximately 75% of patients were likely nausea prone and approximately 25% of patients were possibly nausea prone. Approximately half of the patients had PONV. The majority of patients had moderate pain at baseline.

**Table 6 Demographic and Baseline Characteristics (ITT/Safety Population) – Study 002**

| Parameter | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) |
|---|---|---|---|
| Age, years | | | |
| Mean (SD) | 22.6 (5.3) | 22.3 (4.8) | 22.2 (4.9) |
| Sex, n (%) | | | |
| Female | 156 (73.9) | 149 (72.7) | 32 (64.0) |
| Male | 55 (26.1) | 56 (27.3) | 18 (36.0) |
| Race, n (%) | | | |
| White | 164 (77.7) | 169 (82.4) | 38 (76.0) |
| Black or African American | 22 (10.4) | 15 (7.3) | 9 (18.0) |
| Asian | 13 (6.2) | 13 (6.3) | 2 (4.0) |
| Multiracial | 7 (3.3) | 3 (1.5) | 0 |
| Other | 5 (2.4) | 4 (2.0) | 1 (2.0) |
| Ethnicity, n (%) | | | |
| Not Hispanic or Latino | 162 (76.8) | 165 (80.5) | 44 (88.0) |
| Hispanic or Latino | 49 (23.2) | 40 (19.5) | 6 (12.0) |
| Tobacco use, n (%) | | | |
| Yes | 41 (19.4) | 27 (13.2) | 9 (18.0) |
| No | 170 (80.6) | 178 (86.8) | 41 (82.0) |
| Postoperative nausea and vomiting (PONV), n (%) | | | |
| Yes | 107 (50.7) | 101 (49.3) | 29 (58.0) |
| No | 104 (49.3) | 104 (50.7) | 21 (42.0) |
| Baseline categorical pain intensity scale, n (%) | | | |
| Moderate pain | 146 (69.2) | 148 (72.2) | 42 (84.0) |
| Severe pain | 65 (30.8) | 57 (27.8) | 8 (16.0) |
| Baseline visual analog pain intensity scale | | | |
| Mean (SD) | 72.1 (13.5) | 72.5 (12.4) | 71.7 (12.2) |
| Baseline visual analog pain intensity scale, n (%) | | | |
| ≥ 70 mm | 107 (50.7) | 118 (57.6) | 29 (58.0) |
| < 70 mm | 104 (49.3) | 87 (42.4) | 21 (42.0) |
| Baseline summed NCS score | | | |
| Mean (SD) | 16.5 (12.7) | 15.4 (11.4) | 16.0 (10.5) |
| Panoramic oral X-ray, n (%) | | | |
| Partial bony impaction (>50% bone coverage) | 83 (39.3) | 92 (44.9) | 20 (40.0) |

| Parameter | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) |
|---|---|---|---|
| Full bony impaction (not horizontal) | 106 (50.2) | 95 (46.3) | 22 (44.0) |
| Full bony (horizontally) impaction | 22 (10.4) | 18 (8.8) | 8 (16.0) |
| Number of molar teeth extracted, n (%) | | | |
| >2 molars extracted | 113 (53.6) | 97 (47.3) | 30 (60.0) |
| 2 molars extracted | 98 (46.4) | 108 (52.7) | 20 (40.0) |

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; NCS, Nausea Catastrophizing Scale; SD, standard deviation.
Source: 002 CSR, Table 14.1.3.1.1.

### 6.1.2.1 Clinical Efficacy Results

Co-Primary Endpoints

Study 002 demonstrated clinically and statistically significant efficacy in both co-primary endpoints (analgesia and OINV).

Pain reduction was analyzed using $SPID_{24}$. A higher $SPID_{24}$ score represents greater pain reduction. As illustrated in Figure 9, patients in the CL-108 treatment group had a significantly greater reduction in pain compared with the placebo group (16.2 vs 3.5; $p < 0.001$). The number needed to treat (NNT) for the analgesic endpoint, based on the inverse of the absolute risk difference between CL-108 and placebo, was 5 (95% CI, 3-8). Both CL-108 and Norco were effective analgesics compared with placebo.

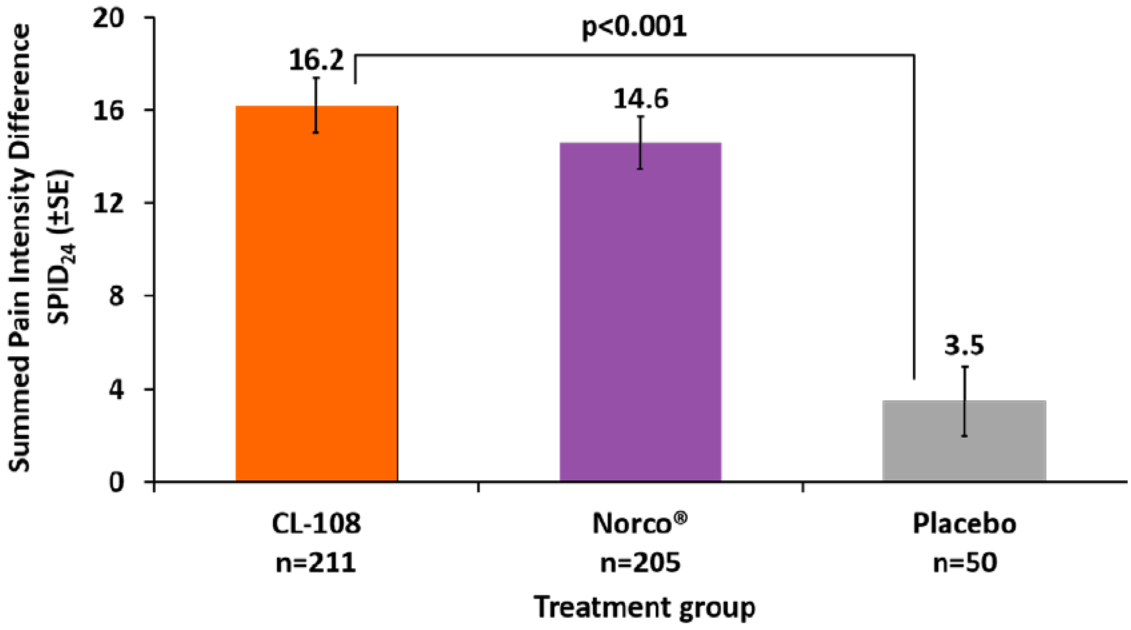


**Figure 9 Analgesia (Pain) Co-Primary Endpoint (ITT Population) – Study 002**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; SE, standard error; $SPID_{24}$, summed pain intensity difference over 24 hours.
Source: 002 CSR, Table 14.2.1.1.

Based on the three-component OINV endpoint, in absolute terms, there was a 22% lower incidence of OINV in the CL-108 treatment group compared with the Norco group ($p < 0.001$; Figure 10). This difference represents a 38% relative reduction in the risk of developing OINV with CL-108. The NNT, based on the inverse of the absolute risk difference between CL-108 and Norco, was 5 (95% CI, 3-8), indicating that for every five patients treated with CL-108 rather than Norco, one less patient will experience OINV.

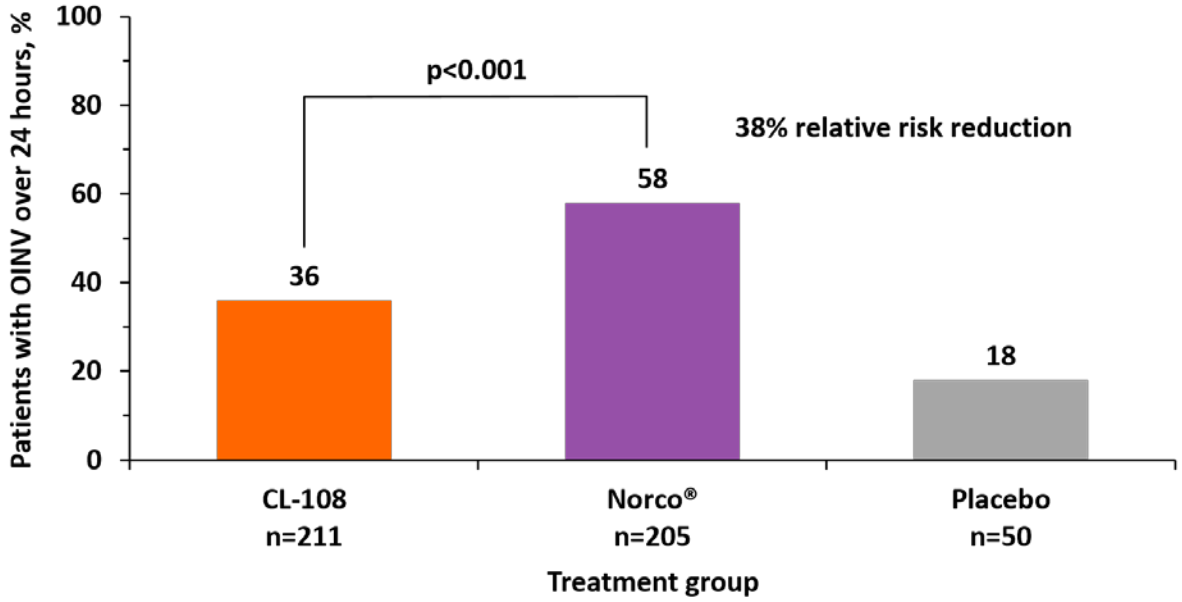


**Figure 10 OINV Co-Primary Endpoint (Three Component; ITT Population) – Study 002**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; OINV, opioid-induced nausea and vomiting.
Source: 002 CSR, Table 14.2.1.1

Additionally, because of FDA feedback on how OINV should be defined, a two-component definition, based on two objective indicators of OINV (use of an antiemetic or any vomiting over 24 hours), was also assessed as a key post-hoc secondary endpoint. By this metric, the relative risk reduction was 64% (Figure 11).

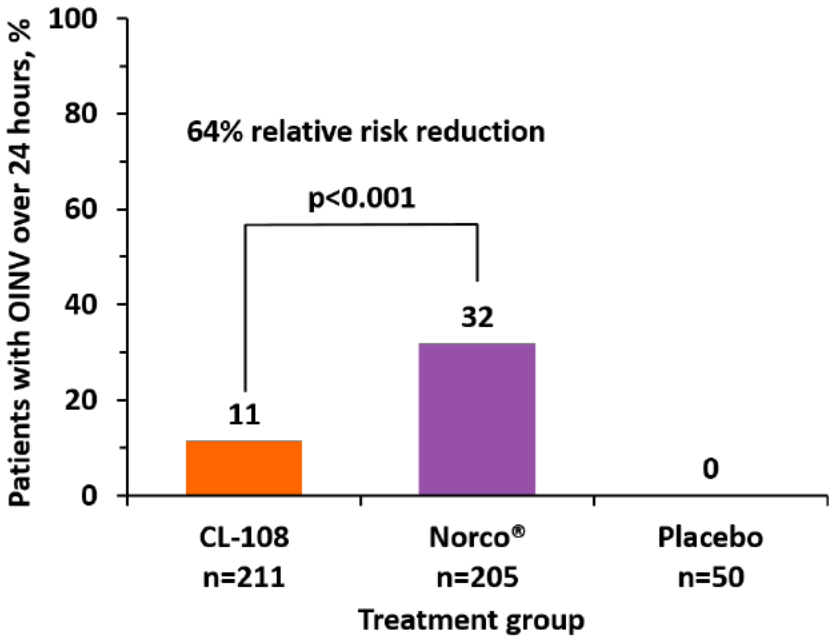


**Figure 11 OINV Endpoint (2 Component; ITT Population) – Study 002**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; OINV, opioid-induced nausea and vomiting.
Source: 002 CSR, Table 14.2.3.7.

Key Secondary Endpoints

Results of the pre-specified key secondary endpoints are summarized in Table 7. Overall, prophylactic antiemetic efficacy was consistent across the key secondary endpoints and further support the co-primary OINV results. A significant reduction in the summed intensity of nausea (on the NIS) was observed over both six-hour ($p < 0.01$) and 24-hour ($p < 0.001$) time periods following CL-108 treatment, compared with Norco. A similar decrease in the summed intensity of nausea was also observed on the StomS for CL-108, compared with Norco ($p < 0.05$). These measures of nausea intensity provide evidence that CL-108 reduces the severity of nausea induced by hydrocodone.

**Table 7 Summary of Key Secondary Endpoints (ITT Population) – Study 002**

| Endpoint | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Summed intensity of nausea (on NIS) | | | | |
| Over 6 hours, mean (SD) | 5.6 (9.0) | 8.3 (12.1) | 3.9 (6.4) | 0.0081 |
| Over 24 hours, mean (SD) | 20.1 (39.2) | 47.2 (62.0) | 8.8 (19.6) | < 0.0001 |
| Summed intensity of nausea (on StomS) | | | | |
| Over 6 hours, mean (SD) | 5.7 (9.0) | 8.2 (11.8) | 3.9 (6.1) | 0.0131 |
| Frequency of vomiting (VFS) | | | | |
| Over 24 hours, mean (SD) | 0.7 (3.3) | 2.4 (7.9) | 0.5 (3.1) | < 0.0001 |

| Endpoint | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Incidence of vomiting or use of antiemetic medication | | | | |
| Over 24 hours, n (%) | 24 (11.4) | 65 (31.7) | NA | < 0.001 |

Abbreviations: ISE, Integrated Summary of Efficacy; ITT, intent-to-treat; NA, not applicable; NIS, Nausea Intensity Scale; SD, standard deviation; StomS, Stomach Scale; VFS, Vomiting Frequency Scale.
Source: ISE Table 13 (Appended ISE Tables 5.1, 5.2, 5.3, 5.4, and 5.5).

## Other Secondary Endpoints

Table 8 and Table 9 summarize other pre-specified secondary OINV and analgesic endpoints, respectively. Consistent with the primary and key secondary OINV findings, these outcomes provided further evidence of reduced severity and frequency of OINV in patients treated with CL-108 over Norco.

**Table 8 Summary of Other Secondary OINV Endpoints – Study 002**

| Endpoint | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| **OINV Endpoint** | | | | |
| Peak intensity of nausea (on NIS) | | | | |
| Over 6 hours, mean (SD) | 2.5 (2.9) | 3.0 (3.2) | 1.6 (1.9) | < 0.05 |
| Over 24 hours, mean (SD) | 3.0 (3.1) | 4.5 (3.4) | 1.7 (1.8) | < 0.001 |
| Over Days 1-5, mean (SD) | 3.4 (3.1) | 4.9 (3.4) | 1.8 (1.9) | < 0.001 |
| Peak nausea intensity (on StomS) | | | | |
| Over 6 hours, mean (SD) | 2.0 (2.7) | 2.6 (3.1) | 1.1 (1.6) | < 0.05 |
| Patients with any moderate-to-severe nausea | | | | |
| Over 6 hours, n (%) | 61 (28.9) | 74 (36.1) | 8 (16.0) | 0.10 |
| Over 24 hours, n (%) | 73 (34.6) | 117 (57.1) | 8 (16.0) | < 0.001 |
| Over Days 1-5, n (%) | 84 (39.8) | 124 (60.5) | 10 (20.0) | < 0.001 |
| Patients with any vomiting (on VFS) | | | | |
| Over 6 hours, n (%) | 13 (6.2) | 21 (10.2) | 1 (2.0) | 0.14 |
| Over 24 hours, n (%) | 21 (10.0) | 43 (21.0) | 2 (4.0) | < 0.01 |
| Over Days 1-5, n (%) | 28 (13.3) | 56 (27.3) | 3 (6.0) | < 0.001 |
| Patients taking supplemental antiemetic medication | | | | |
| Over 5 days, n (%) | 11 (5.2) | 42 (20.5) | 0 | < 0.001 |
| Number of antiemetic doses | | | | |
| Over 24 hours, mean (SD) | 0.0 (0.3) | 0.2 (0.5) | 0 | < 0.001 |
| Patients with complete response | | | | |
| Over 6 hours, n (%) | 84 (39.8) | 64 (31.2) | 20 (40.0) | 0.063 |
| Over 24 hours, n (%) | 68 (32.2) | 40 (19.5) | 17 (34.0) | < 0.01 |

| Endpoint | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Patient satisfaction scale | | | | |
| 6 hours from baseline, mean (SD) | 3.8 (2.2) | 3.4 (2.3) | 2.1 (1.8) | < 0.001[a] |

Abbreviations: CSR, clinical study report; NIS, Nausea Intensity Scale; SD, standard deviation; StomS, Stomach Scale; VFS, Vomiting Frequency Scale.
[a] P value for CL-108 versus placebo.
Source: 002 CSR, Tables 14.2.3.1.1, 14.2.3.2.1, 14.2.3.3.1, 14.2.3.5.1, and 14.2.3.6.1.

**Table 9 Summary of Other Secondary Analgesic Endpoints – Study 002**

| Endpoint | CL-108 (N = 211) | Norco (N = 205) | Placebo (N = 50) | P Value (CL-108 vs Placebo) |
|---|---|---|---|---|
| % Difference in QDPI at 6 hours, mean (SD) | 26.7 (40.4) | 30.6 (37.5) | 6.6 (35.2) | < 0.001 |
| % Maximum TOTPAR4, mean (SD) | 48.1 (23.7) | 49.1 (21.5) | 23.3 (22.7) | < 0.001 |
| % Maximum TOTPAR6, mean (SD) | 44.6 (25.0) | 45.2 (24.4) | 20.7 (22.8) | < 0.001 |
| TOTPAR4, mean (SD) | 7.3 (5.3) | 7.8 (5.2) | 2.8 (4.1) | < 0.001 |
| TOTPAR6, mean (SD) | 11.3 (8.4) | 11.9 (8.6) | 4.3 (6.8) | < 0.001 |
| Patients with ≥ moderate relief over 6 hours, n (%) | 157 (74.4) | 155 (75.6) | 15 (30.0) | < 0.001 |

Abbreviations: CSR, clinical study report; QDPI, Qualities of Dental Pain Index; SD, standard deviation; TOTPARx, total pain relief over x hours.
Source: 002 CSR, Tables 14.2.4.2.1 and 14.2.4.4.1.

Supplemental Medication Use

The number of patients taking any supplemental analgesics over the five-day study period was 133 (63.0%) in the CL-108 group, 136 (66.3%) in the Norco group, and 45 (90.0%) in the placebo group ($p < 0.001$ for CL-108 vs placebo). The median time to taking supplemental analgesics was 33.0 hours in the CL-108 group, 15.6 hours in the Norco group, and 2.2 hours in the placebo group ($p < 0.001$ for CL-108 vs placebo). The percentage of patients taking supplemental antiemetic medication over the five-day study period was significantly greater in the Norco group compared with the CL-108 group (20.5% vs 5.2%; $p < 0.001$).

## 6.2 Study 003

### 6.2.1 Overall Study Design and Methods

#### 6.2.1.1 Study Design

Study 003 was a double-blind, randomized, multiple-dose, placebo- and active-controlled study of CL-108 in patients with moderate-to-severe pain following bunionectomy (with osteotomy and internal fixation) without collateral procedures. Analgesia was determined by comparing CL-108 to placebo. An active control (Norco) was included to determine the antiemetic effects of CL-108.

In this study, up to 550 patients were planned to be enrolled and randomized to one of three treatment groups: CL-108, Norco, or placebo at the ratio of 5:5:1. To enhance assay sensitivity and study efficiency patients who were considered nausea prone by history and fulfilled other entry criteria were admitted if they reported moderate-to-severe pain after bunionectomy. They

remained at the clinic for efficacy and safety assessments for 54 hours, where they were administered one dose of the assigned study medication every 4- to 6-hours (i.e., scheduled dosing), for a maximum of six doses per 24-hour period. This fixed dosing schedule, one dose every 4- to 6-hours, was recommended by DAAAP to ensure that all patients in the CL-108 and Norco treatment groups had the same exposure to hydrocodone over the 48-hour primary treatment observation period. After this period, the next dose of study medication (at 48 hours) was administered while the patient remained at the clinic.

Patients were then discharged home. For outpatient days (Days 3, 4, and 5), patients self-dosed with one dose of the same assigned study medication as needed for pain every 4- to 6-hours, for a maximum of six doses in a 24-hour period. Patients could take supplemental (rescue) medication for pain and/or antiemetic medication anytime according to label directions. Patients who used supplemental medication continued regularly scheduled evaluations of nausea/vomiting and other side effects throughout the entire five-day dosing period. About eight (± two) days after surgery, patients returned to the clinic for final assessments at the end-of-study visit.

The design of Study 003 is illustrated in Figure 12.

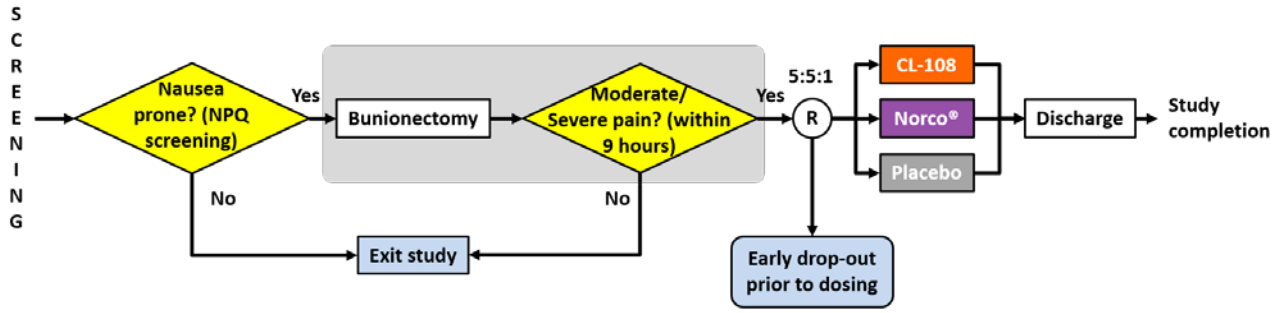


**Figure 12 Study 003 Design Schema**

Abbreviations: NPQ, Nausea Prone Questionnaire; R, randomization.

### 6.2.1.2 Key Eligibility Criteria

Key inclusion criteria were ≥ 18 years of age, at risk of OINV as assessed on the NPQ, primary unilateral first metatarsal bunionectomy (osteotomy and internal fixation) with no additional collateral procedures, moderate-to-severe pain on the PI-CAT and the 0- to 10-point Pain Intensity Numerical Rating Scale (PI-NRS), and willing and able to complete patient diaries. Key exclusion criteria were the presence of a serious medical condition, acute local infection at time of surgery, history of hypersensitivity to opioid drugs, promethazine, acetaminophens, NSAIDs, use of any confounding/contraindicated products within 24 hours, use of investigational drug in the last 30 days, and pregnancy or lactation.

### 6.2.1.3 Endpoints and Analyses

Primary Endpoint

The co-primary endpoints were OINV and analgesia. The co-primary endpoint for OINV was a two-component composite index for the occurrence of OINV comparing CL-108 to Norco over 48 hours: any vomiting or use of antiemetic medication. A patient was considered a responder (i.e., a patient did not have OINV) if he or she experienced no vomiting and used no antiemetic

medication at any time during the 48 hours post-randomization. A patient was considered a nonresponder (i.e., a patient had OINV) if he or she vomited or used antiemetic medication at any time during the 48-hour post-randomization period.

The co-primary analgesia endpoint for a patient was the time-weighted $SPID_{48}$, comparing CL-108 to placebo using results from the PI-NRS. The endpoint was calculated at baseline, every 10 minutes until Hour 2, every 30 minutes until Hour 6, then every hour (while awake) until Hour 48, as follows:

- Each of the subsequent PI-NRS values was subtracted from baseline PI-NRS value.
- Each difference was weighted by the elapsed time from the previous PI-NRS value to the current one.
- The weighted differences were summed to yield the $SPID_{48}$.

For patients who received supplemental medication for pain and/or nausea/vomiting during the 48-hour period of the primary outcome measures, a BOCF convention was used to impute the pain intensity and relief values and a WOCF convention was used to impute nausea/vomiting and other opioid symptoms (OSS) values.

Key Secondary Endpoints

The pre-specified key secondary endpoints comparing CL-108 to Norco included:

- Occurrence of OINV as a three-component endpoint over 48 hours (recommended by DAAAP)
- Use of antiemetics over five days
- Occurrence of vomiting over five days
- Severity of opioid-induced nausea over five days
- Relief of severe pain over 24 hours
- Physician's Global Evaluation (PGE) over 48 hours
- Percentage change in Qualities of Pain Index (QPI) score over 24 hours
- Incidence of post-discharge nausea and vomiting (PDNV) over Days 3 to 5

### 6.2.2 Study 003 Results

#### 6.2.2.1 Patient Disposition

In Study 003, a total of 552 patients were randomized, and most patients completed the study (Table 10). No pregnancies or deaths were reported during the study.

**Table 10 Patient Disposition (ITT/Safety Population) – Study 003**

| Parameter | CL-108 (N = 252) n (%) | Norco (N = 250) n (%) | Placebo (N = 50) n (%) |
|---|---|---|---|
| Treatment status | | | |
| Completed | 249 (98.8) | 241 (96.4) | 47 (94.0) |
| Discontinued | 3 (1.2) | 9 (3.6) | 3 (6.0) |
| Reasons for discontinuation | | | |
| Adverse event | 0 | 1 (0.4) | 0 |
| Lack of efficacy | 1 (0.4) | 2 (0.8) | 1 (2.0) |

| Parameter | CL-108 (N = 252) n (%) | Norco (N = 250) n (%) | Placebo (N = 50) n (%) |
|---|---|---|---|
| Lost to follow-up | 0 | 0 | 0 |
| Noncompliance with study drug | 2 (0.8) | 0 | 0 |
| Withdrawal of consent | 0 | 3 (1.2) | 1 (2.0) |
| Other | 0 | 3 (1.2) | 1 (2.0) |

Abbreviations: ISE, Integrated Summary of Efficacy; ITT, intent-to-treat.
Source: ISE, Table 5 (Appended ISE Table 1.1.2).

#### 6.2.2.2 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics were generally well balanced across the randomized treatment groups (Table 11). Patients were predominantly female and White, and the mean age was approximately 41 years. Most patients had never smoked.

**Table 11 Demographic and Baseline Characteristics (ITT/Safety Population) – Study 003**

| Characteristic | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) |
|---|---|---|---|
| Mean (SD) age, years | 41.2 (13.67) | 41.7 (13.50) | 41.5 (13.52) |
| Sex, n (%) | | | |
| Female | 223 (88.5) | 222 (88.8) | 43 (86.0) |
| Male | 29 (11.5) | 28 (11.2) | 7 (14.0) |
| Race, n (%) | | | |
| White | 220 (87.3) | 220 (88.0) | 46 (92.0) |
| Black or African American | 19 (7.5) | 15 (6.0) | 1 (2.0) |
| Asian | 5 (2.0) | 6 (2.4) | 3 (6.0) |
| Other | 6 (2.4) | 4 (1.6) | 0 |
| Native Hawaiian or Other Pacific Islander | 1 (0.4) | 3 (1.2) | 0 |
| American Indian or Alaska Native | 1 (0.4) | 2 (0.8) | 0 |
| Ethnicity, n (%) | | | |
| Not Hispanic or Latino | 199 (79.0) | 194 (77.6) | 40 (80.0) |
| Hispanic or Latino | 53 (21.0) | 56 (22.4) | 10 (20.0) |
| Tobacco use, n (%) | | | |
| Never used tobacco | 182 (72.2) | 187 (74.8) | 33 (66.0) |
| Past smoker | 45 (17.9) | 43 (17.2) | 14 (28.0) |
| Current smoker | 21 (8.3) | 19 (7.6) | 3 (6.0) |
| Used other forms of tobacco (e.g., e-cigarettes) | 1 (0.4) | 1 (0.4) | 0 |

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; SD, standard deviation.
Source: 003 CSR, Tables 14.1.3.1.1.

Table 12 summarizes pain and nausea assessments at baseline. Pain assessments were similar across the three treatment groups. Most patients had moderate (70.1%) pain at baseline on the PI-CAT. The mean score on the PI-NRS was 6.7, and approximately 50% of patients had a baseline pain intensity $\geq 7$. Most patients had no (74.4%) or mild (20.0%) nausea at baseline when assessed

by N-CAT. Overall, 5.1% of patients had moderate nausea at baseline; one patient in the CL-108 group and two patients in the Norco group had severe nausea before randomization. The majority of patients (72.5%) did not have PONV.

**Table 12 Baseline Pain and Nausea Summary (ITT/Safety Population) – Study 003**

| Characteristic | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) |
|---|---|---|---|
| Baseline Categorical Pain Intensity Scale (PI-CAT), n (%) | | | |
| No pain | 0 | 0 | 0 |
| Mild | 1 (0.4) | 0 | 0 |
| Moderate | 179 (71.0) | 174 (69.6) | 34 (68.0) |
| Severe | 72 (28.6) | 76 (30.4) | 16 (32.0) |
| Baseline Pain Intensity Numerical Rating Scale (PI-NRS) | | | |
| Mean (SD) | 6.6 (1.74) | 6.7 (1.67) | 6.9 (1.77) |
| Baseline PI-NRS, n (%) | | | |
| ≥ 7 | 127 (50.4) | 126 (50.4) | 25 (50.0) |
| < 7 | 125 (49.6) | 124 (49.6) | 25 (50.0) |
| Baseline Qualities of Pain Index (QPI) – overall | | | |
| Mean (SD) | 3.9 (2.08) | 3.9 (2.01) | 4.1 (2.06) |
| Baseline Nausea Intensity Scale (NIS) | | | |
| Mean (SD) | 0.6 (1.39) | 0.7 (1.38) | 0.7 (1.49) |
| Baseline NIS, n (%) | | | |
| ≥ 7 | 3 (1.2) | 2 (0.8) | 0 |
| < 7 | 249 (98.8) | 248 (99.2) | 50 (100) |
| Baseline Nausea Categorical Scale (N-CAT), n (%) | | | |
| None | 185 (73.7) | 184 (73.6) | 41 (82.0) |
| Mild | 51 (20.3) | 52 (20.8) | 7 (14.0) |
| Moderate | 14 (5.6) | 12 (4.8) | 2 (4.0) |
| Severe | 1 (0.4) | 2 (0.8) | 0 |
| Postoperative Nausea and Vomiting (PONV), n (%) | | | |
| Present | 72 (28.6) | 69 (27.6) | 11 (22.0) |
| Absent | 180 (71.4) | 181 (72.4) | 39 (78.0) |

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; SD, standard deviation.
Source: 003 CSR, Table 14.1.3.2.1 and Table 14.1.3.3.1.

### 6.2.2.3 Clinical Efficacy Results

Co-Primary Endpoints

Study 003 demonstrated clinically and statistically significant efficacy in both co-primary endpoints (analgesia and OINV).

For the analgesic co-primary endpoint ($SPID_{48}$), patients in the CL-108 treatment group had a significantly greater reduction in pain compared with the placebo group (118.4 vs 53.1; $p < 0.001$; Figure 13). The NNT for the analgesic endpoint was 4 (95% CI, 3-4).

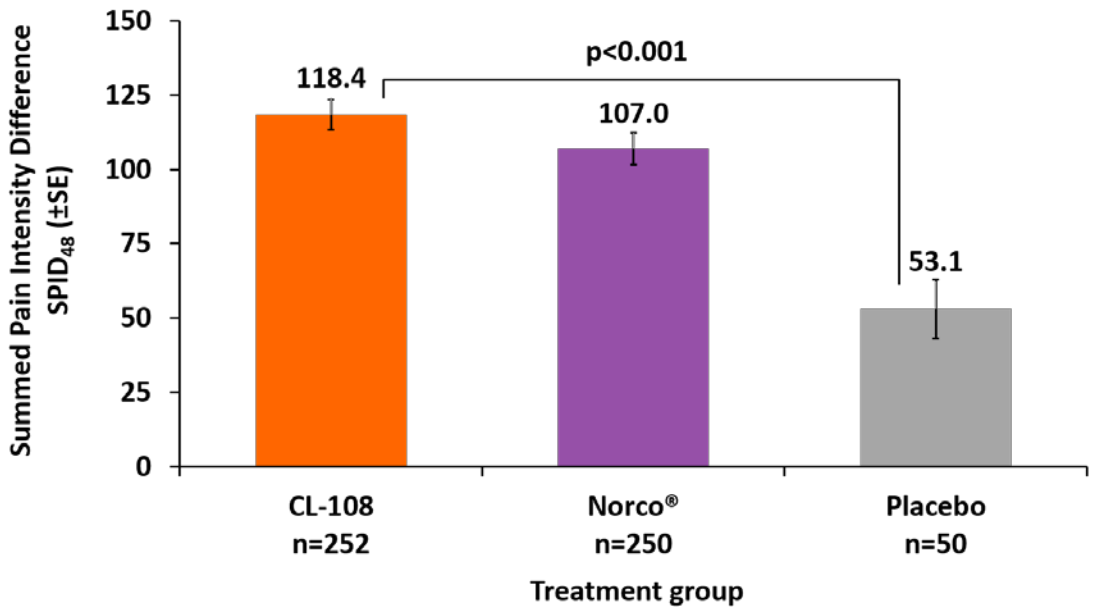


**Figure 13 Analgesia (Pain) Co-Primary Endpoint (ITT Population) – Study 003**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; SE, standard error; $SPID_{48}$, summed pain intensity difference over 48 hours.
Source: Study 003 CSR, Figure 14.2.5.2.

For the OINV co-primary endpoint (based on a two-component definition, described in Section 6.2.1.3), 45.2% of patients in the Norco group compared with 11.9% of patients in the CL-108 group reported OINV ($p < 0.001$; Figure 14). The absolute difference in OINV rate between the groups was 33.3%, indicating a 73.7% (95% CI, 57.4-89.9) relative reduction in the risk of developing OINV for patients treated with CL-108 versus Norco. The NNT for the OINV endpoint was 4 (95% CI, 3-4), indicating that for every four patients treated with CL-108 rather than Norco, one less patient will experience OINV.

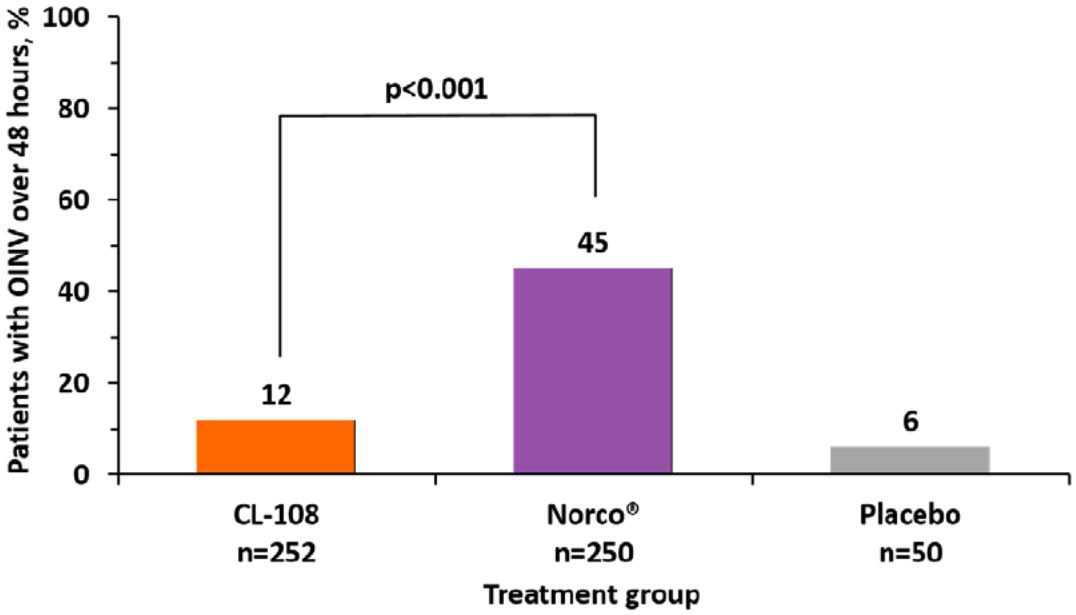


**Figure 14 OINV Co-Primary Endpoint (ITT Population) – Study 003**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; OINV, opioid-induced nausea and vomiting.
Source: Study 003 CSR, Figure 14.2.5.1.

Key Secondary Endpoints

Substantive and consistent clinical responses were also observed across the pre-specified key secondary endpoints (Table 13). As in Study 002, the three-component OINV endpoint showed a significant reduction in the incidence of OINV for patients treated with CL-108 compared with those treated with Norco. Patients who received CL-108 reported significantly milder or no nausea compared to patients who received Norco. The mean incidence of post-discharge nausea/vomiting during outpatient Days 3 through 5 was significantly lower in the CL-108 group versus the Norco group. In addition, the analysis of severe pain relief over 24 hours ($SPID_{24}$) in patients with severe pain at baseline showed CL-108 was approximately 26% more effective than Norco in reducing severe pain ($p = 0.012$).

**Table 13 Summary of Key Secondary Endpoints (ITT Population) – Study 003**

| Endpoint | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Occurrence of OINV as a 3-component endpoint over 48 hours, n (%) | 68 (27.0) | 135 (54.0) | 8 (16.0) | < 0.001 |
| Number of incidents of PDNV over Days 3-5, mean (SD) | 1.1 (2.05) | 3.0 (2.83) | 0.8 (1.82) | < 0.001 |
| Use of antiemetics over 5 days, n (%) | 34 (13.5) | 115 (46.0) | 5 (10.0) | < 0.001 |
| Occurrence of any vomiting over 5 days, n (%) | 21 (8.3) | 61 (24.4) | 1 (2.0) | < 0.001 |
| Severity of opioid-induced nausea (NIS and WNS) over 5 days, mean (SD) | 40.8 (70.24) | 136.1 (179.31) | 28.5 (50.86) | < 0.001 |

| Endpoint | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Relief of severe pain over 24 hours ($SPID_{24}$) for patients with severe pain at baseline, mean (SD) | (n = 127) 55.2 (42.71) | (n = 126) 42.2 (41.18) | (n = 25) 14.9 (28.01) | 0.012 |
| Physician's Global Evaluation (PGE) over 48 hours, mean (SD) | 7.1 (2.04) | 6.8 (2.07) | 5.3 (2.31) | 0.032 |
| Percent change in Qualities of Pain Index (QPI) score over 24 hours, mean (SD) | –45.8 (43.25) | –39.9 (40.01) | –16.2 (40.95) | 0.117 |

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; PDNV, post-discharge nausea and vomiting; SD, standard deviation; WNS, Worst Nausea Scale.
Source: 003 CSR, Table 14.2.2.1.1.

Other Secondary Endpoints

Consistent with the primary and key secondary OINV findings, clinically important findings also emerged for other pre-specified secondary endpoints.

Table 14 shows significant reductions in the peak intensity of nausea, the proportion of patients reporting moderate-to-severe nausea, and the proportion of patients with repeated emetic episodes for those in the CL-108 group compared with the Norco group.

A summary of other pre-specified secondary analgesic endpoints is provided in Table 15. Overall, results for these endpoints confirmed the primary and key secondary analgesic findings.

**Table 14 Summary of Other Secondary OINV Endpoints – Study 003**

| Endpoint | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Peak intensity of nausea (on NIS) | | | | |
| Over 48 hours, mean (SD) | 2.2 (2.85) | 4.2 (3.45) | 1.3 (1.86) | < 0.001 |
| Over 5 days, mean (SD) | 2.6 (2.93) | 4.5 (3.42) | 1.5 (2.01) | < 0.001 |
| Patients with any moderate-to-severe nausea (on NIS) | | | | |
| Over 48 hours, n (%) | 63 (25.0) | 125 (50.0) | 7 (14.0) | < 0.001 |
| Over 5 days, n (%) | 72 (28.6) | 134 (53.6) | 8 (16.0) | < 0.001 |
| Patients with occurrence of vomiting (on RVI) | | | | |
| Over 24 hours, n (%) | 11 (4.4) | 37 (14.8) | 0 | < 0.001 |
| Over 48 hours, n (%) | 15 (6.0) | 56 (22.4) | 0 | < 0.001 |
| Patients with repeat vomiting (on RVI) | | | | |
| Over 48 hours, n (%) | 14 (5.6) | 51 (20.4) | 0 | < 0.001 |
| Over 5 days, n (%) | 18 (7.1) | 53 (21.2) | 1 (2.0) | < 0.001 |
| Patients with any retching (on RVI) | | | | |
| Over 5 days, n (%) | 45 (17.9) | 74 (29.6) | 6 (12.0) | < 0.01 |
| Patients with repeat retching over 5 days (on RVI), n (%) | 32 (12.7) | 61 (24.4) | 4 (8.0) | < 0.001 |
| Patients with retching or vomiting (on RVI) | | | | |
| Over 48 hours, n (%) | 40 (15.9) | 84 (33.6) | 5 (10.0) | < 0.001 |
| Over 5 days, n (%) | 50 (19.8) | 92 (36.8) | 6 (12.0) | < 0.001 |

| Endpoint | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) | P Value (CL-108 vs Norco) |
|---|---|---|---|---|
| Number of episodes of retching or vomiting | | | | |
| Over 48 hours, mean (SD) | 1.5 (5.50) | 5.8 (12.50) | 0.7 (2.94) | < 0.001 |
| Over 5 days, mean (SD) | 1.7 (5.75) | 6.4 (14.22) | 0.8 (3.12) | < 0.001 |
| Patients using antiemetics | | | | |
| Over 24 hours, n (%) | 21 (8.3) | 72 (28.8) | 2 (4.0) | < 0.001 |
| Over 48 hours, n (%) | 27 (10.7) | 106 (42.4) | 3 (6.0) | < 0.001 |
| Over 5 days, n (%) | 34 (13.5) | 115 (46.0) | 5 (10.0) | < 0.001 |
| Patients with repeat use of antiemetics | | | | |
| Over 5 days, n (%) | 12 (4.8) | 77 (30.8) | 3 (6.0) | < 0.001 |
| Relief of PONV | | | | |
| Over 48 hours, mean (SD) | 82.0 (79.52) | 35.9 (101.55) | 118.4 (78.57) | < 0.001 |
| OINV-related sleep disturbances | | | | |
| Day 1, n (%) | 5 (2.0) | 21 (8.4) | 1 (2.0) | < 0.01 |
| Day 2, n (%) | 6 (2.4) | 17 (6.8) | 2 (4.0) | < 0.05 |
| Days 1 and 2 combined, n (%) | 9 (3.6) | 30 (12.0) | 3 (6.0) | < 0.001 |
| Patients with complete response (no nausea, vomiting, or use of antiemetics) | | | | |
| Over 48 hours, n (%) | 108 (42.9) | 48 (19.2) | 24 (48.0) | < 0.001 |
| Over 5 days, n (%) | 89 (35.3) | 40 (16.0) | 22 (44.0) | < 0.001 |
| Patients with complete response (no nausea, vomiting or use of antiemetics) | | | | |
| Over 48 hours, n (%) | 222 (88.1) | 137 (54.8) | 47 (94.0) | < 0.001 |
| Over 5 days, n (%) | 212 (84.1) | 127 (50.8) | 45 (90.0) | < 0.001 |

Abbreviations: CSR, clinical study report; NIS, Nausea Intensity Scale; PONV, postoperative nausea and vomiting; SD, standard deviation; RVI, Retching/Vomiting Index.
Source: 003 CSR, Tables 14.2.3.1, 14.2.3.5, 14.2.3.7, 14.2.3.9, 14.2.3.10, and 14.2.3.11.

## Table 15 Summary of Other Secondary Analgesic Endpoints – Study 003

| Endpoint | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) | P Value (CL-108 vs Placebo) |
|---|---|---|---|---|
| Relief of moderate or severe pain | | | | |
| Over 24 hours ($SPID_{24}$), mean (SD) | 45.7 (38.07) | 37.9 (35.45) | 11.9 (22.49) | < 0.001 |
| Over 48 days ($SPID_{48}$), mean (SD) | 118.4 (80.02) | 107.0 (83.60) | 53.1 (69.69) | < 0.001 |
| % Change in overall evaluative QPI items over 24 hours, mean (SD) | –44.0 (39.13) | –36.7 (40.80) | –17.3 (29.29) | < 0.001 |
| TOTPAR | | | | |
| Over 4 hours, mean (SD) | 11.8 (9.99) | 11.7 (10.35) | 3.2 (6.06) | < 0.001 |
| Over 6 hours, mean (SD) | 17.5 (15.36) | 16.2 (15.15) | 4.3 (8.65) | < 0.001 |
| Over 12 hours, mean (SD) | 38.0 (29.45) | 31.6 (29.38) | 8.6 (14.09) | < 0.001 |

| Endpoint | CL-108 (N = 252) | Norco (N = 250) | Placebo (N = 50) | P Value (CL-108 vs Placebo) |
|---|---|---|---|---|
| Patients with ≥ moderate relief | | | | |
| Over 6 hours, n (%) | 173 (68.7) | 175 (70.0) | 13 (26.0) | < 0.001 |
| Over 12 hours, n (%) | 207 (82.1) | 192 (76.8) | 19 (38.0) | < 0.001 |

Abbreviations: CSR, clinical study report; QPI, Quality Pain Index; SD, standard deviation; SPIDx, summed pain intensity differences over x hours on PI-NRS; TOTPAR, total pain relief.
Source: 003 CSR, Tables 14.2.3.2, 14.2.3.3.1, and 14.2.3.17.

Exploratory Analysis

The observed effect of CL-108 on the development of OINV prompted Charleston to examine whether OINV interferes with pain control. To avoid any confounding that promethazine might have on the relationship between OINV and pain reduction, a post-hoc analysis was conducted on results from Study 003 $SPID_{48}$ outcomes. The $SPID_{48}$ scores in Norco-treated patients who developed OINV (n = 113) were compared with $SPID_{48}$ scores in Norco-treated patients who did not develop OINV (n = 137). As shown in Table 16, mean $SPID_{48}$ scores were approximately 40% lower in Norco-treated patients with OINV than in Norco-treated patients without OINV ($p < 0.001$). These results suggest that OINV adversely effects the analgesic benefits of Norco. Results of this analysis have been accepted for presentation at the 2018 Annual Scientific Meeting of the American Pain Society.

**Table 16 Exploratory Analysis of $SPID_{48}$ in Norco-Treated Patients With or Without OINV – Study 003**

| $SPID_{48}$ | Patient Groups | |
|---|---|---|
| | OINV | No OINV |
| N | 113 | 137 |
| Mean (SD) | 77.7 (69.48) | 131.2 (86.69) |
| Median | 65.5 | 129.2 |
| Min, Max | –2, 380 | –12, 356 |
| LS Means and 95% CI (difference between patient groups) | –49.1 (–68.2 to –30.0) | |
| P value | < 0.001 | |

Abbreviations: CI, confidence interval; CSR, clinical study report; LS, least squares; Max, maximum; Min, minimum; OINV, opioid-induced nausea and vomiting; SD, standard deviation; $SPID_{48}$, summed pain intensity difference over 48 hours.
Source: 003 CSR, Table 20.2.17.22.10.

Supplemental Medication Use

The number of patients taking any supplemental analgesics over the five-day study period was 193 (76.6%) in the CL-108 group, 190 (76.0%) in the Norco group, and 50 (100.0%) in the placebo group ($p = 0.952$ for CL-108 vs placebo). The median time to taking supplemental analgesics was 12.2 hours in the CL-108 group, 7.3 hours in the Norco group, and 2.0 hours in the placebo group ($p < 0.001$ for CL-108 vs placebo).

The percentage of patients taking supplemental antiemetic medication over the five-day study period was significantly greater in the Norco group than in the CL-108 group (46.0% vs 13.5%; $p < 0.001$).

## 6.3 Clinical Efficacy Conclusions

Overall, efficacy results from the two pivotal Phase 3 studies (Studies 002 and 003) demonstrate that CL-108 prevents and reduces the incidence and severity of OINV while relieving moderate-to-severe acute pain. Both studies met their co-primary endpoints and all OINV-related key secondary endpoints. The pattern of results was consistent across multiple rating scales and endpoints, indicating a strong treatment effect of CL-108. Moreover, an exploratory analysis suggests that OINV interferes with pain relief and that the prevention and reduction of OINV may have a secondary benefit (i.e., better pain management). The substantive benefit of CL-108 in terms of OINV prevention (64% to 74% relative risk reduction) highlights the need for an IR opioid that can effectively address this complication in patients who require opioid treatment. If approved, CL-108 can meaningfully improve short-term pain management in patients receiving IR opioids who are at risk for OINV.

# 7.0 CLINICAL EFFECTIVENESS

Study 006 was designed primarily as an actual-use safety study and secondarily to evaluate the effectiveness of CL-108 in patients with osteoarthritis (acute flare) of the knee or hip under actual conditions of use. Overall, patients experienced significant reduction in knee and hip pain and stiffness, resulting in statistically significant improvement in activities of daily living (functions such as getting dressed, bathing and walking). These findings under conditions of actual use support the consistent evidence of efficacy and safety of CL-108 demonstrated in the pivotal Phase 3 trials.

## 7.1 Study 006

### 7.1.1 Overall Study Design and Methods

#### 7.1.1.1 Study Design

Study 006 was a Phase 3, multicenter, single-arm, open-label, actual-use study to evaluate the safety and effectiveness of CL-108 administered on an as-needed basis (every 4- to 6-hours) for the treatment of moderate-to-severe acute pain associated with flares of osteoarthritis of the knee and/or hip. Patients who were dissatisfied with their current NSAID treatment were screened for eligibility for 14 days prior to the baseline assessment on Day 0. Patients were examined and a knee or hip X-ray or X-ray report was reviewed by the Principal Investigator or Subinvestigator to confirm the diagnosis of osteoarthritis of the signal joint (an X-ray of the knee or hip was obtained for Visit 1 if none had been taken in the past). Patients with clinically normal or acceptable laboratory tests were instructed to discontinue their NSAID treatment. Diary data were obtained during Screening, and patients who reported moderate or severe pain on the Arthritis Pain Scale (APS) indicative of a flare of osteoarthritis of the knee or hip were eligible for the trial. After confirmation of eligibility, patients completing Visit 2 assessments and questions 3-12 of the RAND 36-item health survey questionnaire (RHS) were sent home with a two-week supply of CL-108 tablets (90 tablets). They were instructed to take one tablet as needed every 4- to 6-hours as needed for pain in the knee and/or hip (up to six tablets every 24 hours) over the next two weeks and to record those times in the outpatient diary. The Study Coordinator telephoned the patient three days (± two days) later to inquire about the patient's condition and use of the diary. Each evening (9:00 PM ± 15 minutes), the patients also recorded in the diary their arthritis pain and stiffness as well as any side effects they experienced that day. Within 15 to 18 days after Visit 2, patients were required to return to the clinic for a brief in-clinic evaluation (Visit 3). Upon reviewing the patient's diary and his/her experience with the study medication over the two-week treatment period (e.g., effectiveness and tolerability, pill count), the Investigator provided on the PGE an overall assessment of the study medication as a treatment for osteoarthritis.

All patients were then discharged from the study. Post-study telephone follow-up was performed for any patients reporting ongoing adverse effects; repeat laboratory testing of any clinically significant abnormalities was performed at the Investigator's discretion. Otherwise, routine care was provided according to standard clinical practice by the patient's usual health care provider.

#### 7.1.1.2 Key Eligibility Criteria

Patients ≥ 18 years of age with a diagnosis of osteoarthritis of the knee and/or hip were eligible if they were dissatisfied with NSAID treatment due to poor pain control or intolerability, had no

previous use of opioids for osteoarthritis, and experienced moderate-to-severe pain of their signal joint during an acute flare of osteoarthritis with onset within 14 days.

#### 7.1.1.3 Endpoints and Analyses

Safety Endpoints

Safety endpoints included spontaneously reported treatment-emergent adverse events (TEAEs) and changes from baseline to end of treatment in vital signs, electrocardiograms, physical examination and laboratory testing. Safety endpoints were summarized descriptively; TEAE incidence was summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Special attention was given to incidence of opioid-related symptoms.

Efficacy Endpoints

Efficacy endpoints included the PGE, change in pain intensity on the APS after 14 days, change in intensity of joint stiffness on Arthritis Stiffness Evaluation scale after 14 days, percentage of patients satisfied with the study medication on the Satisfaction Scale (SATIS), and change/percentage change in activities (questions 3-12 of the RHS). Efficacy endpoints were summarized descriptively; testing for statistical significance of changes from baseline was performed where appropriate.

### 7.1.2 Study 006 Results

#### 7.1.2.1 Patient Disposition

A total of 179 patients were enrolled, of whom 178 received drug and returned for an assessment (99.4%; Table 17). The one patient excluded from the ITT and Safety Populations was enrolled and had study drug dispensed but decided not to participate and returned all study drug unused. A high proportion of patients completed the study; only five patients discontinued before study end.

**Table 17 Patient Disposition – Study 006**

| Disposition Category | Total n (%) |
|---|---|
| Enrolled | 179 (100) |
| Safety Population | 178 (99.4) |
| ITT Population | 178 (99.4) |
| Per Protocol Population | 162 (90.5) |
| Patients who completed study | 174 (97.2) |
| Patients who discontinued from study | 5 (2.8) |
| Reasons for discontinuation from study | |
| Adverse event | 2 (40.0) |
| Withdrawal requested by patient (AE related) | 1 (20.0) |
| Investigator decision (pre-existing laboratory findings) | 1 (20.0) |
| Protocol violation | 0 |
| Other (lost to follow-up) | 1 (20.0) |

Abbreviations: CSR, clinical study report; ITT, intent-to-treat.
Source: Study 006 CSR, Table 14.1.1.

#### 7.1.2.2 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics are summarized in Table 18. Overall, patients were predominantly female (62.4%) and White (85.4%), and the mean age was 61.2 years. Nearly two thirds of patients had never used tobacco. Radiographic disease assessment at baseline using the Kellgren-Lawrence Grade showed that 69.1% of patients had Grade 2 or 3 osteoarthritis of the knee (Grade 2 joint space narrowing, Grade 3 presence of osteophytes). Eight patients did not have radiographic assessments reported at baseline. The painful target joint was approximately equally distributed between the left and right knee or the left and right hip. Nearly half (46.1%) of patients reported moderate pain, and 53.4% reported severe pain at baseline.

**Table 18 Demographic and Baseline Characteristics (ITT/Safety Population) – Study 006**

| Characteristic | Total (N = 178) |
|---|---|
| Mean (SD) age, years | 61.2 (10.13) |
| Sex, n (%) | |
| Female | 111 (62.4) |
| Male | 67 (37.6) |
| Race, n (%) | |
| White | 152 (85.4) |
| Black or African American | 26 (14.6) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 150 (84.3) |
| Hispanic or Latino | 28 (15.7) |
| Tobacco use, n (%) | |
| Current | 29 (16.3) |
| Past | 33 (18.5) |
| None | 116 (65.2) |
| Kellgren-Lawrence Grade, n (%) | |
| Possible osteophytic lipping (Grade 1) | 28 (15.7) |
| Joint space narrowing (Grade 2) | 67 (37.6) |
| Presence of osteophytes (Grade 3) | 56 (31.5) |
| Sclerosis or bony deformity (Grade 4) | 19 (10.7) |
| Not listed on report | 8 (4.5) |
| Location of the most painful joint, n (%) | |
| Right knee | 85 (47.8) |
| Left knee | 72 (40.4) |
| Right hip | 10 (5.6) |
| Left hip | 11 (6.2) |
| Categorical Pain Scale Score, n (%) | |
| Mild pain | 1 (0.6) |
| Moderate pain | 82 (46.1) |
| Severe pain | 95 (53.4) |

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; SD, standard deviation.
Source: Study 006 CSR, Table 14.1.2.1 and Table 14.1.2.2.

#### 7.1.2.3 Effectiveness Results

Physician's Global Evaluation (PGE)

At the end of treatment (Visit 3), study physicians were asked to rate CL-108 on a 5-point scale. Figure 15 shows that more than half of physicians rated CL-108 as "very good" (33.3%) or "excellent" (21.5%) as a treatment for osteoarthritis.

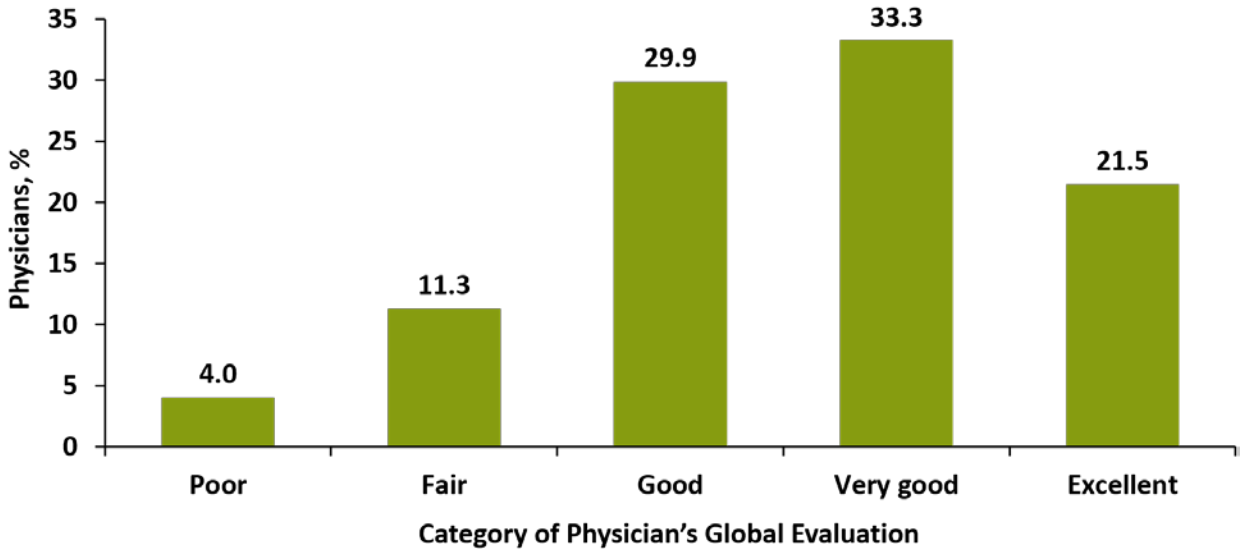


**Figure 15 Physician's Global Evaluation – Study 006 (ITT Population)**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat.
Source: Study 006 CSR, in-text Figure 5 (Table 14.2.1.1).

Pain Intensity and Joint Stiffness

Every night during the two-week treatment observation period, each patient evaluated the average pain experienced over the past 24 hours in his/her affected knee or hip using the APS and recorded it in the outpatient diary.

Compared with pretreatment, CL-108 significantly reduced joint pain in 70.2% of all patients with flares of osteoarthritis ($n = 178$; $p < 0.0001$) and in 80.0% of patients with severe joint pain due to flares of osteoarthritis ($n = 95$; $p < 0.0001$; Figure 16).

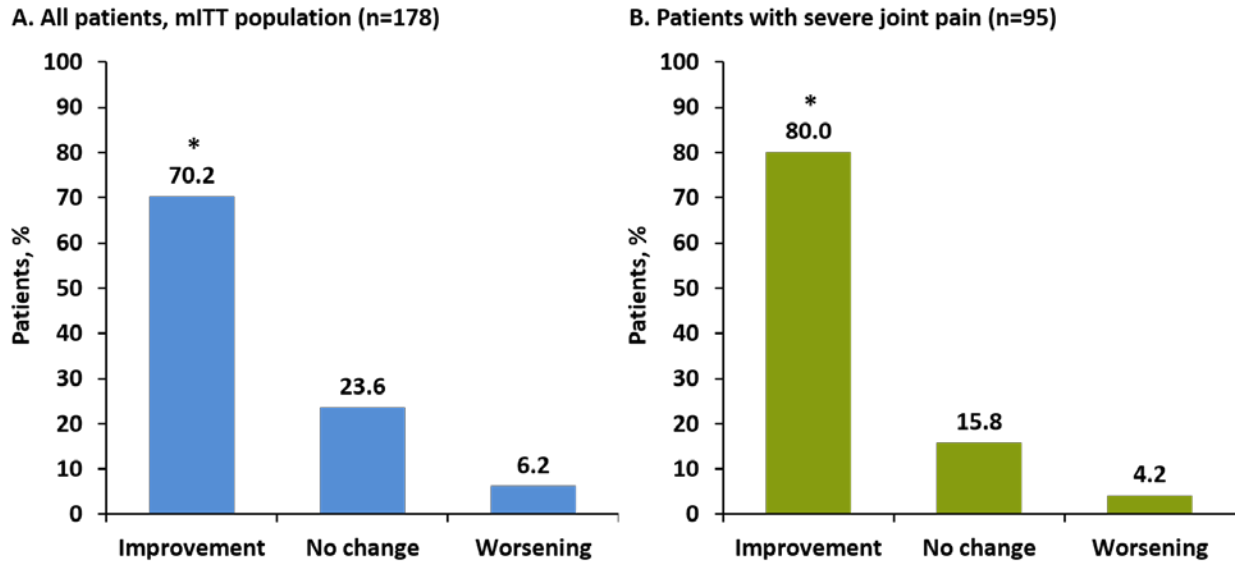


**Figure 16 Change in Joint Pain After As-Needed Treatment With CL-108 for Acute Flares of Osteoarthritis – Study 006**

Abbreviations: CSR, clinical study report; mITT, modified intent-to-treat.
*p < 0.0001 compared with pretreatment.
Source: Study 006 CSR, Table 14.2.4.1.1 and Table 14.2.4.1.3.

Compared with pretreatment, CL-108 also significantly reduced joint stiffness in 65.2% of all patients with flares of osteoarthritis (n = 178; p < 0.0001) and in 86.6% of patients with severe joint stiffness due to flares of osteoarthritis (n = 67; p < 0.0001; Figure 17).

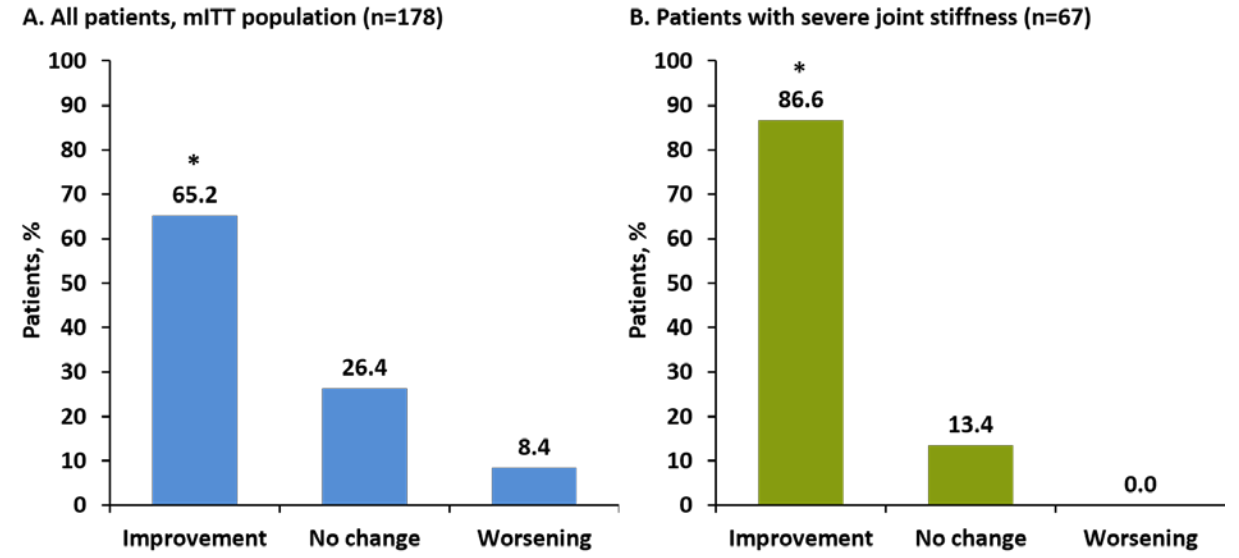


**Figure 17 Change in Joint Stiffness After As-Needed Treatment With CL-108 for Acute Flares of Osteoarthritis – Study 006**

Abbreviations: CSR, clinical study report; mITT, modified intent-to-treat.
*p < 0.0001 compared with pretreatment.
Source: Study 006 CSR, Table 14.2.4.2.1 and Table 14.2.4.2.3.

Patient Satisfaction Scores

Patients were asked to rate their satisfaction with their pre-study NSAID treatment at baseline and after the 14-day treatment period. Satisfaction was rated using the SATIS questionnaire. The categories of response were: (–2) = Very Dissatisfied; (–1) = Dissatisfied; (0) = Somewhat Satisfied; (+1) = Satisfied; (+2) = Very Satisfied. Compared with NSAID treatment at Screening, 94.8% of patients reported greater satisfaction with CL-108 treatment ($p < 0.0001$; Figure 18).

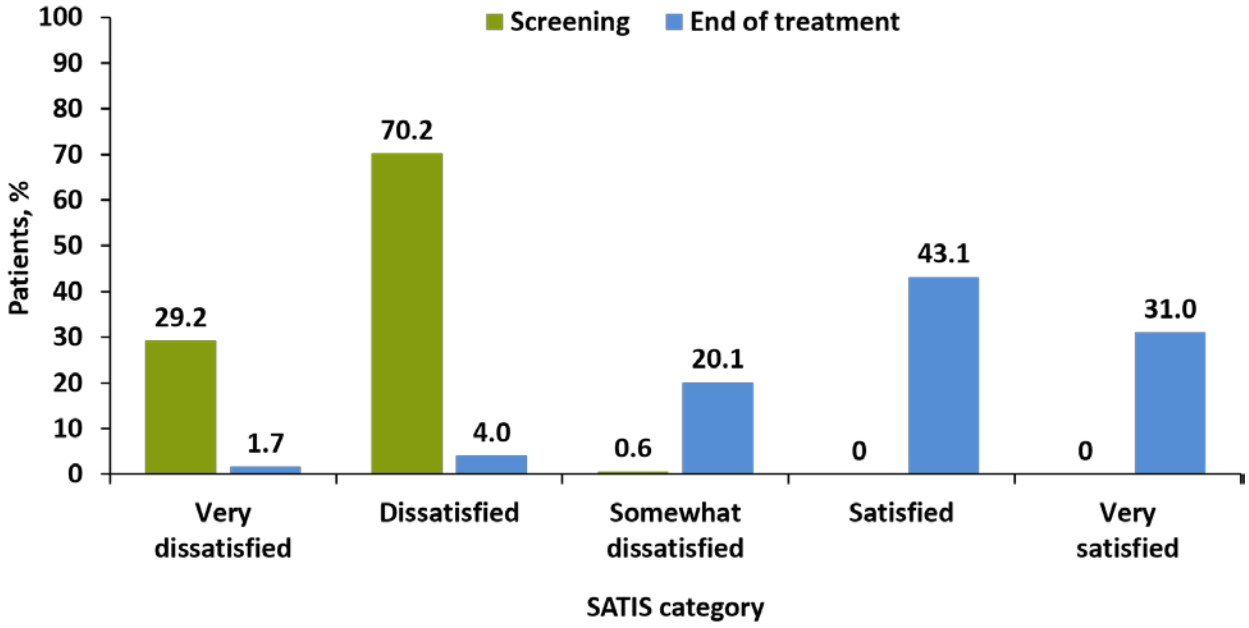


**Figure 18 Patient Satisfaction After CL-108 Treatment Compared With NSAID Treatment at Screening – Study 006 (ITT Population)**

Abbreviations: CSR, clinical study report; ITT, intent-to-treat; SATIS, Satisfaction Scale.
Source: Study 006 CSR, Table 14.2.3.2.1.

Change in RAND 36-Item Health Survey Scores

Examining all patient responses on the RHS showed approximately 21% improvement in general health during the treatment period, where improvement was defined as the RHS score increasing by ≥ 2 points; no change was defined as a change of –1, 0, or 1 point; and worsening was defined as a decrease in RHS score of ≥ 2 points. Compared to their general health during the acute flare, this represented approximately 28% relative improvement in the patients' assessments of their general health after treatment with CL-108.

Total activities were improved approximately 23% after treatment with CL-108. There was at least 20% improvement in specific activities (e.g., climbing one flight of stairs, walking several blocks). In particular, the ability to walk one block (approximately 31% improvement) and the ability to bathe/dress oneself (approximately 39% improvement) represented significant improvements from pretreatment function (all $p < 0.0001$).

## 7.2 Clinical Effectiveness Conclusions

Overall, in this older-aged population (mean age, 61 years) with typical comorbid medical conditions and concomitant medications, the actual use of CL-108 significantly reduced knee and hip pain and stiffness, resulting in a significant improvement in activities of daily living (functions such as getting dressed, bathing, or walking). These findings under conditions of actual use further support the consistent evidence of efficacy demonstrated in the pivotal Phase 3 trials.

# 8.0 CLINICAL SAFETY

The safety and tolerability of CL-108 is well characterized based on data from more than 700 patients who were exposed to the to-be-marketed formulation of CL-108 across the clinical program, including two pivotal Phase 3 efficacy and safety studies (Studies 002 and 003), an open-label, Phase 3 actual-use safety study (Study 006), and three bioavailability studies (Studies 004, 012, and 013). These data are supplemented by safety findings for the RLDs, namely Vicoprofen, Ultracet, and Phenergan, which have manageable and predictable safety profiles. No new specific safety concerns were identified during the pivotal Phase 3 studies, the actual-use safety study, or in any of the dedicated clinical pharmacology studies. Overall, the clinical program demonstrated that CL-108 was generally well tolerated, with side effects that were mostly mild or moderate in intensity and limited in duration. No respiratory depression was observed. Adverse events (AEs) such as drowsiness, dizziness, syncope/presyncope, and pyrexia/increased body temperature were observed, but they were predominantly of mild or moderate severity, and none were serious or resulted in discontinuation of study drug. Known AEs that are addressed in the warnings and precautions of the RLDs are also included in the proposed label for CL-108.

## 8.1 Pivotal Efficacy and Safety Studies (Pooled Studies 002 and 003)

This section describes results of the integrated safety analysis from 466 patients in Study 002 and 552 patients in Study 003. Study design, patient population characteristics, and efficacy data have been presented in Section 6.1 for Study 002 and Section 6.2 for Study 003.

### 8.1.1 Safety Assessments and Analyses

A pooled safety analysis was conducted for the two randomized, pivotal trials. In these studies, 11 opioid-related symptoms were assessed. Two of these (nausea and vomiting) were directly measured on rating scales for the composite co-primary OINV efficacy endpoints. The other nine opioid-related side effects, including confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizzy, were captured through active surveillance using the OSS questionnaire (adapted from the validated opioid-related Symptoms Distress Scale [SDS]). Each symptom was rated on individual 0-10 Likert scales (0 = none; 1-3 = mild; 4-6 = moderate; 7-10 = severe). These side effects were reported as secondary endpoints in the two pivotal Phase 3 studies (in agreement with the DAAAP; Pre-IND Meeting Minutes) and therefore they were not "double-counted" as patient-reported AEs in these two trials. The OSS was administered at baseline and periodically following drug administration.

TEAEs other than nausea, vomiting, and the nine other common opioid-related symptoms were documented by conventional spontaneous patient reports. These patient-reported TEAEs are also presented in the pooled analyses for these two studies.

### 8.1.2 Extent of Exposure

In Studies 002 and 003, 463 patients were treated with CL-108 (Table 19). The mean durations of exposure to CL-108, Norco, and placebo were generally similar (4.7, 4.5, and 4.1 days, respectively). A total of 338 patients (73.0%) were exposed to CL-108 for at least five days compared with 63.7% in the Norco group and 58.0% in the placebo group. The mean number of daily doses was determined by taking the total number of tablets taken per day divided by the number of days when at least one tablet was taken during the treatment period. An average of 3.2

tablets of CL-108 were taken daily, and the maximum mean number of CL-108 tablets per day over the treatment period was 4.2 tablets per day. The cumulative number of CL-108 tablets taken over the total treatment period ranged between 1 and 32 tablets, with an average of 15.5 tablets per patient. Similar numbers were reported in the Norco group.

**Table 19 Extent of Exposure – Pooled Studies 002 and 003**

| Parameter | CL-108 (N = 463) | Norco (N = 455) | Placebo (N = 100) |
|---|---|---|---|
| Mean (SD) duration of exposure, days | 4.7 (1.24) | 4.5 (1.36) | 4.1 (1.52) |
| Duration of exposure (categorical), n (%) | | | |
| ≥ 1 day | 463 (100) | 455 (100) | 100 (100) |
| ≥ 3 days | 441 (95.2) | 407 (89.5) | 84 (84.0) |
| ≥ 5 days | 338 (73.0) | 290 (63.7) | 58 (58.0) |
| ≥ 7 days | 17 (3.7) | 18 (4.0) | 2 (2.0) |
| Mean (SD) number of daily doses[a] | 3.2 (0.93) | 3.1 (0.96) | 3.0 (1.04) |
| Mean (SD) maximum number of daily doses[b] | 4.2 (1.14) | 4.1 (1.16) | 4.0 (1.38) |
| Mean (SD) total cumulative dose[c] | 15.5 (6.31) | 14.3 (6.70) | 12.9 (6.78) |

Abbreviations: ISS, Integrated Summary of Safety; SD, standard deviation.
[a] The sum (number of tablets taken per day)/number of days when at least one tablet was taken during the treatment period.
[b] The maximum number of tablets per day over the treatment period.
[c] The sum of tablets taken over the total treatment period.
Source: Appended ISS Tables 2.2.1 and 2.2.2, and Table 78.

### 8.1.3 Opioid-Related Side Effects

In the two pivotal trials, opioid-related symptoms occurred at generally similar rates in the CL-108 and Norco groups (Figure 19). Across the CL-108, Norco, and placebo groups, drowsiness was the most commonly reported symptom (93.1%, 88.6%, and 69.0%, respectively). Headache (70.8%, 72.1%, and 77.0%, respectively) and dry mouth (71.5%, 63.3%, and 53.0%, respectively) were also among the most common AEs, with a high background incidence observed in the placebo group. Consistent with the inclusion of promethazine in CL-108, slightly higher rates of certain CNS events were observed with CL-108 compared with Norco. Most opioid-related side effects were assessed as mild or moderate in intensity and were without sequelae.

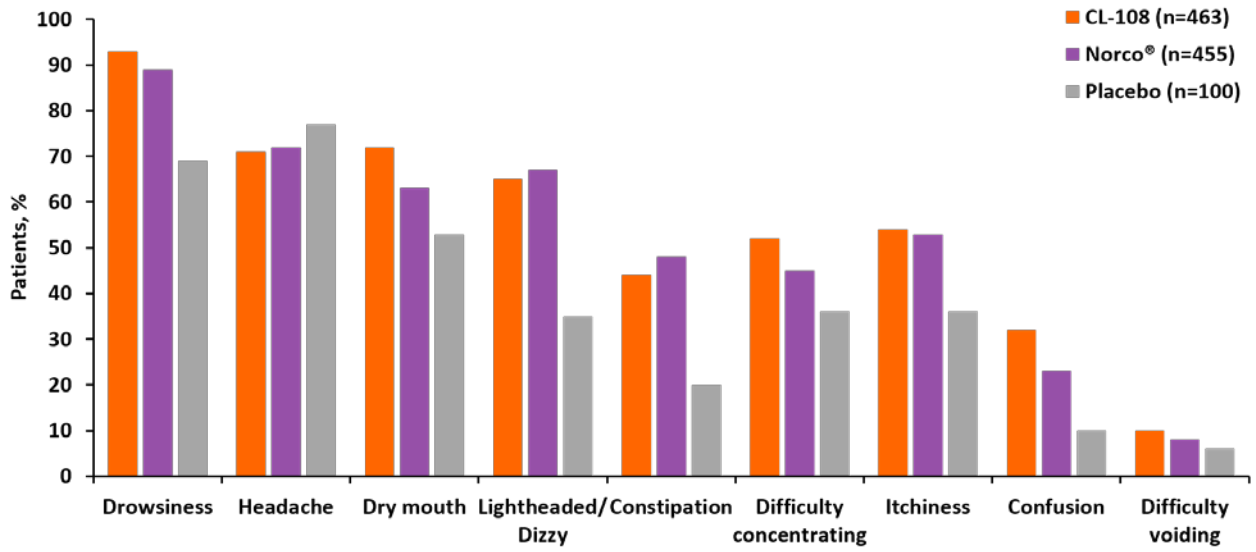


**Figure 19 Opioid-Related Symptoms (OSS) – Pooled Studies 002 and 003**

Abbreviations: ISS, Integrated Summary of Safety; OSS, Opioid Symptom Scale.
Source: Appended ISS Table 2.3.15, Table 23.

Most opioid-related symptoms were mild (i.e., ≤ 3 on the 11-point OSS). Over the five-day treatment period, the mean severity of most opioid-related symptoms was rated as mild in the CL-108 and Norco groups (Figure 20). The exception was drowsiness, for which the mean severity was in the moderate range (4-6). Of note, many patients reported pretreatment drowsiness; in most cases the severity improved over time with continued therapy, and no patient discontinued study drug due to drowsiness. On Day 1, 24.8% of patients in the CL-108 group reported severe drowsiness compared with 16.7% in the Norco group. By Day 5, only 12.1% of patients in the CL-108 group reported severe drowsiness compared with 5.1% in the Norco group.

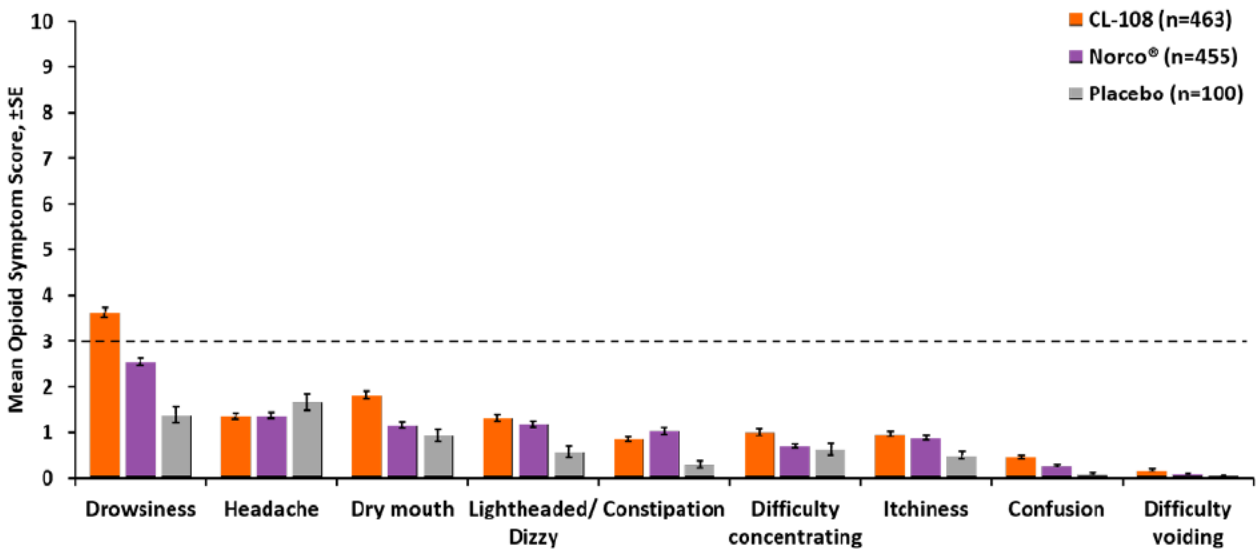


**Figure 20 Severity of Opioid-Related Symptoms (OSS) Over a 5-Day Period – Pooled Studies 002 and 003**

Abbreviations: ISS, Integrated Summary of Safety; OSS, Opioid Symptom Scale.
Source: Appended ISS Table 2.3.15.

### 8.1.4 Treatment-Emergent Adverse Events (Excluding Nausea, Vomiting and Nine Opioid-Related Symptoms)

#### 8.1.4.1 Overall Summary of TEAEs

Excluding opioid-related side effects, the proportion of patients with at least one spontaneously reported TEAE in the pooled Phase 3 studies was similar across all treatment groups (Table 20). There were two patients with treatment-emergent serious adverse events (TESAEs): one patient with breast carcinoma in the CL-108 group and one patient with cellulitis in the Norco group (see Section 8.1.4.3 for details) and neither was assessed as related to study drug. TEAEs were assessed by the investigators as related to the study drug at similar rates in the CL-108, Norco, and placebo groups (6.0% to 6.8%). There were no reported events leading to study drug withdrawal in the CL-108 group and low incidences (≤ 1%) of TEAEs leading to study drug withdrawal in the Norco and placebo groups. For most TEAEs, severity was reported as mild or moderate following treatment in all groups.

**Table 20 Summary of TEAEs (Excluding Nausea, Vomiting, and the Nine Opioid-Related Symptoms) – Pooled Studies 002 and 003**

| Event | CL-108 (N = 463) | Norco (N = 455) | Placebo (N = 100) |
|---|---|---|---|
| Total number of AEs | 167 | 176 | 42 |
| Total number of SAEs, n | 1 | 1 | 0 |
| Total number of patients, n (%) | | | |
| At least 1 AE | 122 (26.3) | 119 (26.2) | 28 (28.0) |
| At least 1 study drug-related AE | 31 (6.7) | 31 (6.8) | 6 (6.0) |
| At least 1 SAE | 1 (0.2) | 1 (0.2) | 0 |

| Event | CL-108 (N = 463) | Norco (N = 455) | Placebo (N = 100) |
|---|---|---|---|
| At least 1 AE leading to study drug withdrawal | 0 | 1 (0.2) | 1 (1.0)[a] |
| Summary of maximum AE severity, n (%) | | | |
| Mild | 68 (14.7) | 65 (14.3) | 22 (22.0) |
| Moderate | 44 (9.5) | 51 (11.2) | 5 (5.0) |
| Severe | 10 (2.2) | 3 (0.7) | 1 (1.0) |

Abbreviations: AE, adverse event; ISS, Integrated Summary of Safety; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a] This patient had an event of tooth avulsion during surgery before study drug administration.
Source: Appended ISS Table 2.3.1.

### 8.1.4.2 Most Frequently Reported TEAEs

In the pooled Studies 002 and 003, the common TEAEs (occurring in ≥ 1% of patients in the active treatment group) were typical of what is expected with an opioid analgesic and were generally similar across all groups, although some occurred at a numerically higher frequency in the CL-108 group (Table 21).

**Table 21 Summary of Common (≥ 1%) TEAEs by PT (Excluding Nausea, Vomiting, and the Nine Opioid-Related Symptoms) – Pooled Studies 002 and 003**

| Preferred Term | CL-108 (N = 463) n (%) | Norco (N = 455) n (%) | Placebo (N = 100) n (%) |
|---|---|---|---|
| Total number of TEAEs | 50 | 60 | 42 |
| Subjects with at least 1 TEAE | 49 (10.6) | 54 (11.9) | 28 (28.0) |
| Alveolar osteitis | 8 (1.7) | 17 (3.7) | 2 (2.0) |
| Body temperature increased | 6 (1.3) | 0 | 0 |
| Pyrexia | 5 (1.1) | 1 (0.2) | 3 (3.0) |
| Syncope | 5 (1.1) | 0 | 1 (1.0) |
| Abdominal pain upper | 2 (0.4) | 5 (1.1) | 1 (1.0) |
| Decreased appetite | 0 | 8 (1.8) | 0 |

Abbreviations: ISS, Integrated Summary of Safety; PT, preferred term; TEAE, treatment-emergent adverse event.
Source: Appended ISS Table 2.3.3.

In the pooled pivotal studies, severe TEAEs were uncommon. Except for the event of pain in extremity reported in two patients, all other severe TEAEs in the CL-108 group were reported in one patient each.

In the pooled pivotal studies, treatment-related TEAEs were reported in 31 patients (6.7%) in the CL-108 group, in 31 patients (6.8%) in the Norco group, and in six patients (6.0%) in the placebo group. In the CL-108, Norco, and placebo groups, respectively, the most common (> 2 patients in each group) treatment-related TEAEs were abnormal dreams (3 vs 1 vs 0 patients), presyncope and syncope (3 vs 0 vs 0), abdominal pain upper (1 vs 3 vs 1), hot flush (0 vs 1 vs 0), decreased appetite (0 vs 7 vs 0), and dyspnea (0 vs 3 vs 0).

#### 8.1.4.3 Deaths and Other Serious Adverse Events

No patient died during either of the pivotal studies.

Two patients who received treatment reported serious adverse events (SAEs). One patient in the CL-108 group had breast carcinoma and one patient in the Norco group had cellulitis (see brief narratives below). Neither event was considered related to study drug by the Investigator.

- A 45-year-old female patient in the CL-108 group (in Study 003) had an SAE of infiltrating ductal breast carcinoma. At a routine office visit with her physician in 2013, a mammogram revealed a suspicious lesion, and the decision was made at that time to follow-up at the patient's next annual visit. She received the first dose of study drug (CL-108) on December 17, 2014, and the last dose on December 19, 2014. Twelve days after the last dose of study treatment, at an annual primary care visit to the doctor, the patient had an ultrasound-guided right breast biopsy test positive for infiltrating ductal carcinoma. It was assessed as serious because it was an important medical event. The Investigator considered the infiltrating ductal carcinoma of the right breast to be not related to the study treatment.
- A 41-year-old female in the Norco group (in Study 003) had an SAE of cellulitis. The patient had a left bunionectomy on June 29, 2015, and began treatment with Norco on June 30, 2015, with her last dose on (b) (6). Thirty days after her last dose, she was hospitalized due to cellulitis of that foot. She was treated with intravenous antibiotics and discharged home on the third day. The Investigator considered the cellulitis to be not related to the study medication.

#### 8.1.4.4 TEAEs Resulting in Discontinuation of Study Drug

In the pooled pivotal studies, no TEAE led to early study drug withdrawal in the CL-108 or placebo groups (one patient in the placebo group had an event of tooth avulsion during surgery but prior to study drug administration). One TEAE led to study drug withdrawal in one patient in the Norco group (a 64-year-old female). This event was a burning sensation on the surgical site of the right foot, of moderate intensity, the day after the first dose of study medication. The study medication was withdrawn the following day and the condition resolved that same day. This event was considered unlikely related to the Norco treatment.

#### 8.1.4.5 Events of Special Interest

Adverse events of special interest (AESIs) were defined based on the known effects of hydrocodone and promethazine and on patterns of adverse reactions observed during clinical trials. These events included opioid-related side effects (as described in Section 8.1.3), hypotension/blood pressure decreased, presyncope/syncope, body temperature increase/pyrexia, respiratory depression, abdominal pain, seizure, and tardive dyskinesia.

As shown in Table 22, the incidence of AESIs (excluding opioid-related symptoms) was low or absent. When there was a difference between CL-108 and Norco, the percentages were similar between the CL-108 and placebo groups. Of note, no respiratory depression was reported in any of the treatment groups. Overall, none of the AESIs were deemed severe and none resulted in dose reduction, study drug interruption, discontinuation of study drug, or clinically significant consequences or sequelae. All AESIs resolved without recurrence while on treatment.

**Table 22 Summary of AESIs (Excluding Opioid-Related Symptoms) – Pooled Studies 002 and 003**

| AESIs | CL-108 (N = 463) n (%) | Norco (N = 455) n (%) | Placebo (N = 100) n (%) |
|---|---|---|---|
| Pyrexia/body temperature increased | 11 (2.4) | 1 (0.2) | 3 (3.0) |
| Syncope/presyncope | 8 (1.7) | 0 | 1 (1.0) |
| Abdominal pain | 5 (1.1) | 7 (1.5) | 1 (1.0) |
| Hypotension/blood pressure decreased | 3 (0.6) | 3 (0.7) | 1 (1.0) |
| Respiratory dyspnea | 1 (0.2) | 4 (0.9) | 1 (1.0) |
| Dyskinesia | 1 (0.2) | 0 | 0 |
| Respiratory depression | 0 | 0 | 0 |
| Seizure | 0 | 0 | 0 |

Abbreviations: AESI, adverse event of special interest; ISS, Integrated Summary of Safety.
Source: Appended ISS Section 4.5.

AESIs that occurred at a higher rate with CL-108 than Norco are briefly described below.

- **Pyrexia/body temperature increased—**These TEAEs occurred at a higher rate in the CL-108 group than in the Norco group (2.4% vs 0.2%), but at a similar rate in the CL-108 and placebo groups (2.4% vs 3.0%). Except for two moderate events, all pyrexia and body temperature increased events were of mild severity. Where body temperatures were available at (or around) the time of the event, the maximum reported temperature was 40.3°C. Only one of these events was considered by the Investigator to be treatment-related. This event occurred in the CL-108 group; no other TEAEs were reported for this patient. None of the events were serious. Most events of pyrexia and body temperature increased resolved without sequelae within one to three days, while one event resolved within six days. Overall, no AEs were reported in any of the patients who experienced pyrexia that would be consistent with neuroleptic malignant syndrome (NMS), including mental status change, muscle rigidity, or autonomic dysfunction. Most patients had no other relevant AE. One patient in the CL-108 group had AEs of pain in jaw, ear pain, and local swelling starting just prior to the body temperature increased event. One patient in the Norco group had an AE of oropharyngeal pain concurrent with pyrexia. One patient in the placebo group also had an AE of oropharyngeal pain, post-procedural swelling, hemorrhage, chills, hyperhidrosis, and dehydration within the same timeframe as the pyrexia event.
- **Syncope/presyncope—**TEAEs of syncope were reported in five patients in the CL-108 group, no patients in the Norco group, and one patient in the placebo group. Of these, three patients in the CL-108 group had syncope events considered by the Investigator to be related to study drug. TEAEs of presyncope were reported in three patients in the CL-108 group and in no patients in either the Norco or placebo groups. All presyncope events were considered by the Investigator as treatment-related. None of the syncope or presyncope events were serious. All AEs of syncope and presyncope resolved without recurrence or sequelae with continued study treatment. The patients with AEs of syncope or presyncope did not have other relevant AEs such as hypotension or lightheadedness/dizziness. There was no clear correlation between decreases in blood pressure and syncope/presyncope events.

## 8.2 Actual-Use Safety Study (Study 006)

This section describes safety findings of the open-label, single-arm, actual-use safety study. Study design, patient population characteristics, and effectiveness/patient satisfaction data have been presented in Section 7.1.

### 8.2.1 Safety Assessments and Analyses

In Study 006, patients were not screened for their previous conditions or OINV, and the OSS questionnaire was not administered. Instead, all AEs, including nausea, vomiting, and other opioid-related side effects, were captured through diary entries in a nondirective fashion throughout the 14-day treatment period.

### 8.2.2 Extent of Exposure

In Study 006, 178 adult patients were instructed to take one tablet of CL-108 as needed every 4- to 6-hours for pain in the knee and/or hip (up to six tablets over 24 hours). The treatment period was 14 days. The mean duration of exposure to CL-108 was 14.7 ± 3.13 days, and the mean number of daily doses received was 2.0 ± 1.2. The maximum duration of exposure of 23 days. The largest proportion of patients (64.6%) was treated for more than 14 days given the time allowance for scheduling the final study visit.

### 8.2.3 Treatment-Emergent Adverse Events

#### 8.2.3.1 Overall Summary of TEAEs

Table 23 summarizes different types of TEAEs in Study 006. Overall, few patients discontinued study drug due to TEAEs, and only one patient experienced an SAE, which was not considered related to study drug. No deaths were reported.

**Table 23 Summary of TEAEs – Study 006**

| Adverse Event Parameter | CL-108 (N = 178) n (%) |
|---|---|
| Patients who had a TEAE | 84 (47.2) |
| Patients who had a treatment-related TEAE | 65 (36.5) |
| Patients who had an SAE | 1 (0.6) |
| Patients who had a TEAE leading to study drug discontinuation | 3 (1.7) |
| Patients who had a TEAE leading to death | 0 |

Abbreviations: CSR, clinical study report; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Source: 006 CSR, Table 14.3.1.1.

#### 8.2.3.2 Most Frequently Reported TEAEs

In Study 006, individual AEs with a frequency ≥ 5% included somnolence (18.0%) and dizziness (10.7%; Table 24). Of the 84 patients who reported TEAEs, the majority had events of mild or moderate severity, and approximately one third (36.5%) were considered related to study drug.

**Table 24 Summary of Common (≥ 2%) TEAEs by PT – Study 006**

| Preferred Term | CL-108 (N = 178), n (%) | | |
|---|---|---|---|
| | All TEAEs | Severe TEAEs | Related TEAEs |
| Subjects with at least 1 event | 84 (47.2) | 11 (6.2) | 65 (36.5) |
| Somnolence | 32 (18.0) | 2 (1.1) | 32 (18.0) |
| Dizziness | 19 (10.7) | 1 (0.6) | 17 (9.6) |
| Constipation | 8 (4.5) | 1 (0.6) | 8 (4.5) |
| Fatigue | 8 (4.5) | 0 | 7 (3.9) |
| Dry mouth | 5 (2.8) | 1 (0.6) | 5 (2.8) |
| Headache | 5 (2.8) | 0 | 5 (2.8) |
| Nausea | 4 (2.2) | 0 | 4 (2.2) |
| Pruritus | 4 (2.2) | 2 (1.1) | 2 (1.1) |
| Urinary tract infection | 4 (2.2) | 0 | 1 (0.6) |

Abbreviations: CSR, clinical study report; PT, preferred term; TEAE, treatment-emergent adverse event.
Source: 006 CSR, Tables 14.3.1.2, 14.3.1.3, and 14.3.1.4.

#### 8.2.3.3 Deaths and Other Serious Adverse Events

No patient died during this study.

One patient in this study experienced an SAE. This patient underwent a surgical procedure during the treatment period (elective bilateral breast reconstruction, previously scheduled but not revealed at enrollment) and developed a breast flap occlusion. Details of this surgery and postsurgical complication were reported only at the last study visit; the event was considered unrelated to study treatment, and the patient recovered without sequelae.

#### 8.2.3.4 TEAEs Resulting in Discontinuation of Study Drug

Three patients had TEAEs that resulted in discontinuation of study drug:

- One patient was a 53-year-old White female with ongoing knee pain from osteoarthritis diagnosed in 1994. The patient was enrolled on October 6, 2014. Study medication was taken once daily from October 10, 2014 (Study Day 1) to October 12, 2014, for a total of seven doses with an inter-dose interval of 8.3 ± 2.4 hours (mean ± SD). The patient experienced treatment-emergent repeated episodes of mild nausea with mild hyperhidrosis starting on Study Day 2 and continuing intermittently until Study Day 3, when moderate nausea and moderate hyperhidrosis were reported. No action was taken regarding study drug until Day 3 (October 12, 2014) when study drug was discontinued because of both moderate nausea and mild hyperhidrosis. All AEs resolved without sequelae and without additional concomitant medications. Study medication was discontinued permanently. The Investigator assessed the events of moderate nausea with mild hyperhidrosis as probably related to study drug.
- One patient was an 84-year-old White female with ongoing hip pain from osteoarthritis, diagnosed in 2012. The patient was enrolled on October 28, 2014, and received a single dose of study drug CL-108 on November 8, 2014. The patient experienced a fall (moderate severity) on November 10, 2014 (Study Day 3) with a concurrent laceration (moderate), and chest wall injury (moderate). No other TEAEs were reported just prior to or after the time of the fall. The

patient recovered from the fall and chest wall injury with no sequelae; the laceration was presumably healing at the time of discontinuation. Study medication was discontinued permanently at the patient's request. The patient was also prescribed a different analgesic hydrocodone/acetaminophen, 5/325 mg orally, as needed for two days without known sequelae. The Investigator assessed the events of fall, laceration, and chest wall injuries as not related to the study drug.

- One patient was a 64-year-old White female with ongoing knee pain from osteoarthritis diagnosed in 2011. The patient was enrolled on October 15, 2014. Study medication was taken once daily from October 22, 2014 (Study Day 1) to October 25, 2014 (Study Day 4) for a total of four doses. TEAEs reported around the time of the event included mild dizziness, severe abdominal discomfort, severe tachycardia, and severe somnolence; all reported as starting on Study Day 1 and ending on Study Day 4 with no action taken regarding study drug. The patient experienced severe diarrhea from October 25, 2014, to October 26, 2014 (Study Day 4 to Day 5) requiring discontinuation of study drug. Study medication was discontinued permanently. All AEs resolved without sequelae and without additional concomitant medications. The Investigator assessed the events of severe abdominal discomfort, severe tachycardia, severe somnolence, and severe diarrhea as probably related to study drug. The event of mild dizziness was considered possibly related to study drug.

### 8.2.3.5 Opioid-Related Side Effects

A total of 185 AEs commonly associated with opioids were reported by 81 patients (45.5%). Most events were mild to moderate in severity. The most frequently reported events were drowsiness and lightheaded/dizziness, without adverse sequelae despite continued self-dosing (Figure 21). The incidence of drowsiness and dizziness generally tended to decrease across the 14 days of treatment. Four patients reported nausea, including one patient who also reported vomiting, resulting in an OINV incidence of 2.2%.

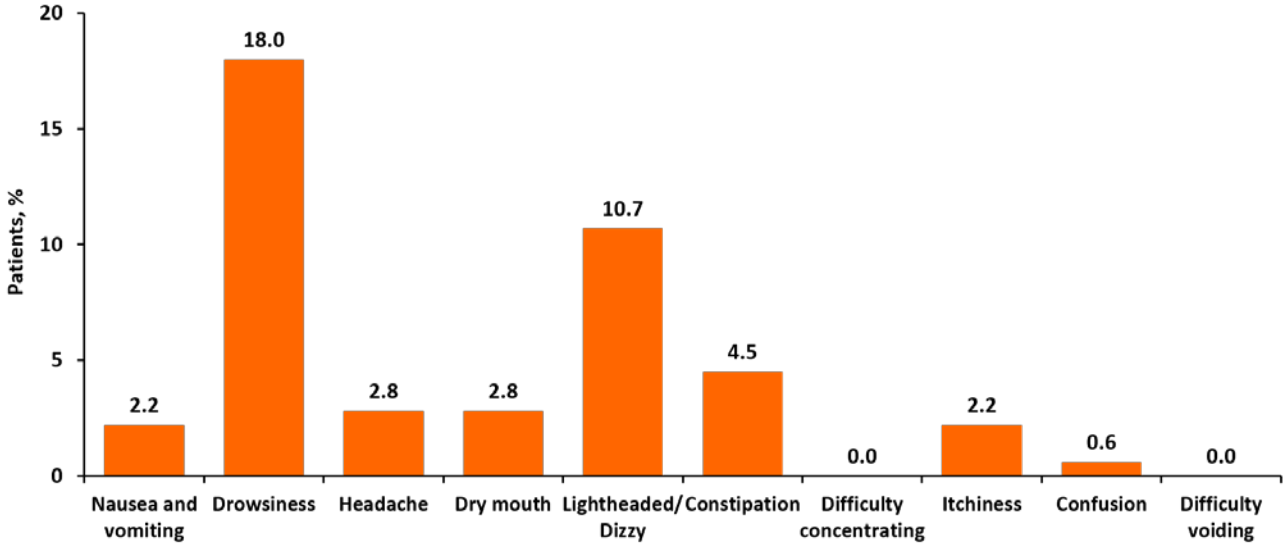


**Figure 21 Frequency of Spontaneously Captured Opioid-Related Symptoms – Study 006**

Abbreviations: CSR, clinical study report.
Source: 006 CSR, In-Text Figure 13.

## 8.3 Bioavailability Studies (Studies 004, 012, and 013)

### 8.3.1 Study 004

#### 8.3.1.1 Extent of Exposure

Nineteen of 20 subjects enrolled were administered all scheduled doses of the test product CL-108 tablet (administered under fasted conditions [Treatment A] or fed conditions [Treatment B]) and comparator product (hydrocodone bitartrate and ibuprofen tablet, 7.5 mg/200 mg; promethazine HCl tablet, USP, 12.5 mg; and Ultracet tablet) (administered under fasted conditions [Treatment C] or fed conditions [Treatment D]). Dosing in the four study periods was separated by a 14-day washout period. The total dose administered to each subject who completed all four study periods was 30 mg of hydrocodone bitartrate, 1,300 mg of acetaminophen, 50 mg of promethazine, 400 mg of ibuprofen, and 75 mg of tramadol. Ibuprofen and tramadol were not analyzed in this study.

#### 8.3.1.2 Treatment-Emergent Adverse Events

Table 25 shows the rates of TEAEs following each treatment. Three subjects (15.8%) reported an AE after receiving Treatment A, five subjects (20.0%) after Treatment B, eight subjects (40.0%) after Treatment C, and two subjects (10.5%) after Treatment D. There were no deaths or other SAEs, and no subject discontinued from study drug due to an AE. The most commonly observed TEAE was nausea under fasted conditions: nausea was reported by one subject (5.3%) after Treatment A and by four subjects (20.0%) after Treatment C. The second most commonly observed AE under fasted conditions was dizziness, which was reported by one subject (5.3%) after Treatment A and by three subjects (15.0%) after Treatment C.

The most commonly observed AE under fed conditions was somnolence, which was reported by one subject (5.0%) after Treatment B and by two subjects (10.5%) after Treatment D. The second most commonly observed AEs under fed conditions (all after Treatment B) were nausea, headache, and hypotension—each reported by two subjects (10.0%).

Hypotension under fasted conditions was reported by three subjects (15.0%) after Treatment C. One AE of orthostatic hypotension was reported after Treatment B. AEs of hypotension and orthostatic hypotension were considered of clinical significance by the Investigator.

**Table 25 Frequency of TEAEs After Each Treatment by PT – Study 004**

| Preferred Term | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Treatment A (N = 19) | Treatment B (N = 20) | Treatment C (N = 20) | Treatment D (N = 19) |
| Nausea | 1 (5.3) | 2 (10.0) | 4 (20.0) | 0 |
| Dizziness | 1 (5.3) | 1 (5.0) | 3 (15.0) | 0 |
| Somnolence | 0 | 1 (5.0) | 2 (10.0) | 2 (10.5) |
| Hypotension | 0 | 2 (10.0) | 3 (15.0) | 0 |
| Headache | 0 | 2 (10.0) | 1 (5.0) | 0 |
| Hot flush | 0 | 0 | 2 (10.0) | 0 |
| Diarrhea | 0 | 1 (5.0) | 0 | 0 |
| Dry mouth | 1 (5.3) | 0 | 0 | 0 |
| Glossodynia | 0 | 0 | 1 (5.0) | 0 |

| Preferred Term | Number (%) of Subjects | | | |
|---|---|---|---|---|
| | Treatment A (N = 19) | Treatment B (N = 20) | Treatment C (N = 20) | Treatment D (N = 19) |
| Oral pruritus | 0 | 0 | 1 (5.0) | 0 |
| Vomiting | 0 | 0 | 1 (5.0) | 0 |
| Vessel puncture site pain | 0 | 0 | 1 (5.0) | 0 |
| Euphoric mood | 0 | 0 | 1 (5.0) | 0 |
| Hyperhidrosis | 0 | 1 (5.0) | 0 | 0 |
| Orthostatic hypotension | 0 | 1 (5.0) | 0 | 0 |

Abbreviations: CSR, clinical study report; PT, preferred term; TEAE, treatment-emergent adverse event.
Treatment A: CL-108 (7.5 mg hydrocodone bitartrate/325 mg acetaminophen/12.5 mg promethazine) under fasted conditions.
Treatment B: CL-108 (7.5 mg hydrocodone bitartrate/325 mg acetaminophen/12.5 mg promethazine) under fed conditions.
Treatment C: Hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg tablet + Ultracet tablet (tramadol HCl 37.5 mg/acetaminophen 325 mg) + promethazine HCl 12.5 mg tablet (all three tablets taken together) under fasted conditions.
Treatment D: Hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg tablet + Ultracet tablet (tramadol HCl 37.5 mg/acetaminophen 325 mg) + promethazine HCl 12.5 mg tablet (all three tablets taken together) under fed conditions.
Source: 004 CSR, Table 14.3.1.2.

### 8.3.2 Study 012

#### 8.3.2.1 Extent of Exposure

Thirty-one of 32 subjects enrolled were administered both scheduled doses (single dose of CL-108 in one period and a separate single dose of Norco in another period). Dosing in the two study periods was separated by a washout period of at least seven days. The total dose administered to each subject who completed both study periods was 15 mg of hydrocodone, 650 mg of acetaminophen, and 12.5 mg of promethazine.

#### 8.3.2.2 Treatment-Emergent Adverse Events

Table 26 provides an overview of the TEAEs in Study 012. A total of 23 TEAEs were reported by 11 subjects during the study. There was also one non–treatment-emergent AE. No SAEs occurred, and no AEs led to study drug discontinuation or death. Most AEs resolved by the end of the study without intervention.

**Table 26 Summary of Adverse Events – Study 012**

| Parameter | CL-108 n (%) | Norco n (%) |
|---|---|---|
| Number of subjects dosed | 32 | 31 |
| Subjects with an AE | 8 (25.0) | 6 (19.4) |
| Subjects with a treatment-related AE | 7 (21.9) | 6 (19.4) |
| Subjects with an AE leading to study drug discontinuation | 0 | 0 |
| Subjects with a treatment-related AE leading to study drug discontinuation | 0 | 0 |
| Subjects with an SAE | 0 | 0 |

Abbreviations: AE, adverse event; CSR, clinical study report; SAE, serious adverse event.
Source: 012 CSR, Table 14.3.1.1.

The most common AEs were somnolence (reported by three subjects [9.4%] after administration of CL-108 and by two subjects [6.5%] after administration of Norco) and nausea (reported by two

subjects [6.3%] after CL-108 and by three subjects [9.7%] after Norco). The second most common AE was hypotension, with four occurrences in three subjects (9.4%), all after administration of CL-108.

The Investigator judged two AEs (nausea after administration of Norco and hypotension after administration of CL-108) as moderate in severity and all other AEs as mild.

### 8.3.3 Study 013

#### 8.3.3.1 Extent of Exposure

Thirty of the 32 subjects enrolled were administered both scheduled doses (single dose of CL-108 in one period and a separate single dose of Norco in another period). Dosing in the two study periods was separated by a washout period of at least seven days. The total dose administered to each subject who completed both study periods was 15 mg of hydrocodone, 650 mg of acetaminophen, and 12.5 mg of promethazine.

#### 8.3.3.2 Treatment-Emergent Adverse Events

Table 27 provides an overview of the TEAEs in Study 013. Sixteen TEAEs were reported by 10 subjects during the study. There was also one non–treatment-emergent AE. No SAEs occurred, and no AEs led to a study drug discontinuation or death. All AEs resolved by the end of the study, most without intervention.

**Table 27 Summary of Adverse Events – Study 013**

| Parameter | CL-108 n (%) | Norco n (%) |
|---|---|---|
| Number of subjects dosed | 30 | 32 |
| Subjects with an AE | 7 (23.3) | 6 (18.8) |
| Subjects with a treatment-related AE | 7 (23.3) | 4 (12.5) |
| Subjects with an AE leading to study drug discontinuation | 0 | 0 |
| Subjects with a treatment-related AE leading to study drug discontinuation | 0 | 0 |
| Subjects with an SAE | 0 | 0 |

Abbreviations: AE, adverse event; CSR, clinical study report; SAE, serious adverse event.
Source: 013 CSR, Table 14.3.1.1.

The most common AE was somnolence, reported by six subjects (20.0%) after administration of CL-108. The second most common AE was dizziness, reported by three subjects (9.4%) after administration of Norco and one subject (3.3%) after administration of CL-108.

The Investigator judged two AEs (somnolence and myalgia after administration of CL-108) as moderate in severity and all other AEs as mild.

## 8.4 Postmarketing Safety Assessment

### 8.4.1 Safety Profile of Promethazine

Promethazine is a phenothiazine derivative with anti-allergic, antiemetic, and sedative properties. It is a first-generation antihistamine and a weak neuroleptic. Promethazine is currently available in a wide range of dosages and oral formulations for the treatment of allergies, motion sickness,

and nausea/vomiting, as well as for sedation and pre/postoperative use. It is also available in injectable formulations. Reports of promethazine-induced respiratory depression led to the addition of a black box warning to its label, stating that promethazine should not be used in children less than two years of age because of the potential for fatal respiratory depression.[16,67-70] An additional black box warning was added to indicate that caution should be exercised when administering promethazine to pediatric patients greater than two years of age. These warnings apply to all formulations of promethazine, including syrups, suppositories, tablets, and injectables.

Other warnings associated with promethazine use include CNS depression, respiratory depression, lower seizure threshold, bone marrow depression, and NMS.[16,67-69] These events are briefly described below.

- *CNS depression*—Promethazine may impair the mental and/or physical abilities required or the performance of potentially hazardous tasks. Impairment may be amplified by concomitant use of other CNS depressants such as alcohol, sedatives/hypnotics (including barbiturates), narcotics, narcotic analgesics, general anesthetics, tricyclic antidepressants, and tranquilizers. Such agents should either be eliminated or given in reduced dosage.
- *Respiratory depression*—Promethazine may lead to potentially fatal respiratory depression. Use of promethazine in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease [COPD], sleep apnea) should be avoided.
- *Lower seizure threshold*—Promethazine may lower the seizure threshold; should be used with caution in persons with seizure disorders or in persons who are using concomitant medications that may also affect seizure threshold.
- *Bone marrow depression*—Promethazine should be used with caution in patients with bone marrow depression; leukopenia and agranulocytosis have been reported, usually when promethazine has been used in association with other known marrow-toxic agents.
- *Neuroleptic malignant syndrome (NMS)*—A potentially fatal symptom complex that may include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability.

The most common adverse reactions of promethazine affect the GI system (dry mouth, epigastric distress, loss of appetite, nausea, vomiting, constipation, diarrhea), nervous system (sedation, restlessness, dizziness, lassitude, incoordination, fatigue), and ocular system (blurred vision).[16,67-69]

Oral promethazine DDIs include CNS depressants, epinephrine, anticholinergics, and monoamine oxidase inhibitors (MAOIs).[16,67-69] Promethazine may increase, prolong, or intensify the sedative actions of other CNS depressants, and it may reverse epinephrine's vasopressor effect. Concomitant use of promethazine and other agents with anticholinergic properties should be approached with caution. An increased incidence of extrapyramidal symptoms (EPS) have been reported with concomitant use of some MAOIs and promethazine.

EPS is a very infrequent but serious side effect of promethazine.[71-75] The rate of reported tardive dyskinesia in the FDA Adverse Event Reporting System (FAERS) database is similar in patients receiving promethazine and not hydrocodone (0.0031) and in those receiving neither promethazine nor hydrocodone (0.0024). Moreover, a PubMed search did not reveal any literature regarding promethazine dose versus continued administration in relation to EPS.

In general, low-dose oral formulations of promethazine (as in CL-108) are not associated with the same level of risk for EPS and severe CNS side effects as high-dose or intravenous promethazine formulations. In addition, because promethazine, a phenothiazine derivative, contains phenol and

has an alkaline pH of approximately 4.0 to 5.5, it can be damaging to veins and tissues if used parenterally.[76,77] Product labeling warns against subcutaneous and intra-arterial injection of promethazine as it can cause serious vascular, nerve, and soft-tissue injury.[78] Nevertheless, the proposed CL-108 label will carry all the same warnings and precautions as the respective RLD labels.

### 8.4.2 FAERS Analysis of Hydrocodone and Promethazine Combination

A thorough review of the FAERS database from 1968 through the fourth quarter of 2016 was conducted to examine the nine predefined safety outcomes (PSOs) that could potentially be exacerbated by the combination of hydrocodone and promethazine. The nine PSOs were tardive dyskinesia, cognitive impairment, respiratory depression, reduction in seizure threshold, syncope, torsade de pointes, pyrexia and NMS, hypotension, and somnolence. Given that there is no standard for assessing for potential DDI using the FAERS database, five analytical methods were employed. The additive and multiplicative models from Thakrar and colleagues were preselected as the primary analyses.[79] Two ad hoc exploratory analyses used Multi-item Gamma Poisson Shrinker disproportionality scores: one 2-dimensional (for the drug term and the predefined safety outcome), and one 3-dimensional (for hydrocodone, promethazine and the predefined safety outcome). The last ad hoc exploratory analysis was a computation of a multivariate disproportionality score using logistic regression.

Overall, results do not suggest safety concerns beyond what is already addressed in the proposed CL-108 proposed label. The primary analyses were not consistent: the more sensitive and predictive additive model found no DDIs for the nine PSOs, while the multiplicative model highlighted DDI scores for NMS and the convulsions narrow SMQ (standardized MedDRA query), based on very small numbers. This is likely a false finding for multiple reasons.

The ad hoc exploratory analyses did not support the findings from the multiplicative method and only syncope and presyncope appeared in more than one of these ad hoc analyses. Syncope and presyncope was also seen at a higher rate with CL-108 vs Norco in clinical trials and is included as a warning (under severe hypotension) and a clinical trial adverse drug reaction in the proposed label. In summary, there are no new safety concerns from this FAERS evaluation that are not addressed in the updated, proposed label for CL-108.

## 8.5 Clinical Safety Conclusions

Clinical study results involving more than 770 patients exposed to CL-108 demonstrated that the safety and tolerability of CL-108 are consistent with its individual components and their established safety profiles. In the pivotal Phase 3 trials, TEAE rates were comparable across treatment groups, and most events were mild to moderate in severity and did not increase in frequency or severity with continued dosing. No new safety signals were identified. Opioid-related symptoms occurred at generally similar rates in the CL-108 and Norco groups, and drowsiness was the most common. In most cases, the severity of drowsiness improved over time with continued therapy, and no patient discontinued study drug as a result. The pivotal study results are further supported by the actual-use safety study that allowed as-needed exposure over 14 days. None of the opioid-related symptoms or AESIs (hypotension/blood pressure decreased, presyncope/syncope, body temperature increase/pyrexia, respiratory depression, abdominal pain, seizure, and tardive dyskinesia) resulted in death, hospitalization, discontinuation or reduction of

study medication, or worsened with repeated dosing. Therefore, the proposed label for CL-108 will carry the same warnings and precautions as the RLD labels.

In addition to the CL-108 safety analysis, a thorough review of FAERS from 1968 through 2016, which examined the nine PSOs that could potentially be exacerbated by the combination of hydrocodone and promethazine, concluded that there are no new safety concerns that are not addressed in the proposed label for CL-108. Finally, our ongoing reviews of the literature from Q1 2010 through Q4 2016 revealed no findings that would require changes in the safety profile of hydrocodone or promethazine.

In summary, the clinical trial safety observations, FAERS analysis, and postmarketing literature review, in addition to the 50-plus years of clinical experience with the individual components of CL-108, represent an extensive base of experience to assess the safety of CL-108.

# 9.0 ABUSE POTENTIAL AND HUMAN ABUSE LIABILITY

The addition of promethazine to hydrocodone may cause concerns regarding increased abuse potential. Promethazine itself can be abused, both alone and in combination with opioids, and concerns have been raised that promethazine may add to the abuse potential of hydrocodone. Therefore, a HAL study was conducted to evaluate whether combining promethazine with hydrocodone in CL-108 would have greater abuse potential.

## 9.1 Epidemiology of Promethazine Abuse

The abuse potential of promethazine and how it is used in conjunction with opioids has been explored, and studies have concluded that promethazine itself has a low abuse potential and is rarely abused alone.

The first documented medical use of an opioid in combination with promethazine dates back to the 1950s. In 1961, Mepergan™ for injection, consisting of meperidine (Demerol™) and promethazine, was approved in the United States as an anesthetic. However, there are no published studies investigating its abuse potential. A supplemental NDA for Mepergan Injection was submitted by West-Ward Pharmaceuticals and was approved by the FDA in 2016. Mepergan Injection is indicated for (1) the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate; and (2) as a preanesthetic medication when analgesia and sedation are indicated, and as an adjunct to local and general anesthesia.[80] The dosing guidance is to use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. Mepergan Injection adult dosing 1 to 2 mL (25 to 50 mg of each component [meperidine and promethazine]) per single injection, which can be repeated every three to four hours.

The first reports of an opioid being abused in combination with an antihistamine date back to the 1970s. Since the 1990s, there have been reports of cough syrup containing codeine and promethazine being abused to achieve feelings of euphoria.[81] However, most of the abuse may be driven by the opioid, in this instance codeine, rather than the promethazine.

There are some regional examples of promethazine being used in conjunction with heroin/opioids. Reports suggest that drug abusers combine substances to potentiate or extend the feelings of euphoria. Although promethazine could be seen, prima facie, as a desirable product to combine with opioids or benzodiazepines, there is limited evidence to suggest that promethazine potentiates the high from opioids.

Several studies specifically designed to investigate the abuse of promethazine in combination with opioids have been reported. For example, a study of 921 chronic pain patients in San Francisco observed that approximately 9% tested positive for promethazine, yet only half of those who tested positive had an active prescription for promethazine. In addition, patients having benzodiazepine-positive urine but no active prescription for a benzodiazepine was statistically associated with promethazine use. Of note, patients prescribed a long-acting opioid were more likely to test positive for promethazine than patients prescribed a short-acting opioid.[82] Novak et al.[83] also conducted a national study of intravenous heroin/opioid users and found that promethazine was being combined with opioids largely to achieve a "runway" effect. Intravenous heroin/opioid users reported self-administering oral promethazine toward the end of a drug using episode (i.e., "run") to ease withdrawal symptoms that included nausea and fidgeting.

Around the world, several studies have investigated the prevalence of promethazine and opioid co-consumption. Dahlman et al[84] concluded that the low rate of promethazine observed in a sample of patients with opioid use disorder suggests that the "nonmedical use of antihistaminergic anxiolytics does not seem to be a clinical issue among people in [opioid maintenance treatment] in a Swedish setting." In one of the most comprehensive reviews of the abuse potential of promethazine, Tsay et al.[85] concluded that the data collected from US poison control centers indicated that over a 10-year period, there were only 354 product exposures in their poison control system, with 27% being promethazine alone, although the use of combination products moderately increased the risk of adverse health outcomes, such as drowsiness and tachycardia.

In conclusion, although the available epidemiologic evidence is limited with regard to the prevalence of abuse, promethazine and other antihistamines can be abused in combination with opioids. Given the potential for abuse, the CL-108 label will carry the same black box warning as with all opioids regarding its potential for abuse, misuse, and diversion, and Charleston is committed to ongoing monitoring and surveillance and employing other risk mitigation strategies as described in Section 10.0. To further investigate the specific abuse potential of CL-108, a HAL study was conducted, which demonstrated, similar to Dahlman et al, that promethazine was not associated with an increased abuse potential in recreational drug users.

## 9.2 HAL Study (Study 007)

### 9.2.1 Study Design and Methods

Study 007 was a randomized, double-blind, placebo-controlled, and active-controlled, five-period crossover study in opioid-experienced, nondependent recreational drug users to determine whether the addition of promethazine might affect abuse potential. The study compared CL-108 versus placebo, and versus hydrocodone and acetaminophen without promethazine. Comparisons were made at supratherapeutic doses (three and five times the recommended dose). The primary endpoint was the maximum effect ($E_{max}$) of drug liking on a bipolar visual analog scale (VAS) from 0 to 100, where a score of 50 was neither like nor dislike the effect at the moment. After Screening, subjects were given a naloxone challenge to ensure they were not physically dependent on opioids. After a 12-hour washout period, they received 30 mg hydrocodone with 1,300 mg acetaminophen to determine if they could tolerate the treatment and distinguish it from placebo. Subjects with a 15-point difference on drug liking were randomized to the Treatment Phase of the study wherein they received each of the five treatments in a random sequence. All study medications were over-encapsulated in identical capsules for double-blinding. Assessments were made over 24 hours with a minimum washout period of approximately 72 hours between each treatment.

The design of Study 007 is illustrated in Figure 22.

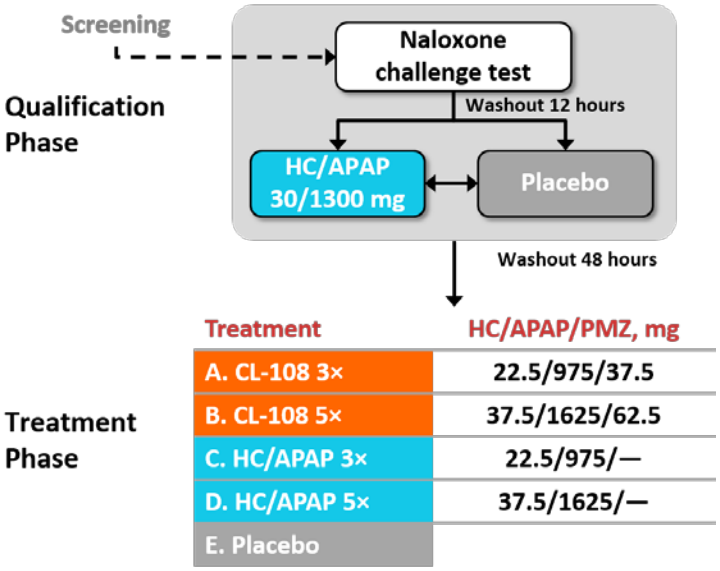


**Figure 22 Study 007 Design Schema**

Abbreviations: APAP, acetaminophen; CSR, clinical study report; HC, hydrocodone; PMZ, promethazine.
Source: 007 CSR, page 23.

### 9.2.2 Patient Disposition

A total of 61 subjects received at least one dose of study drug (not including naloxone) in the Qualification Phase and comprised the Qualification Safety Set. A total of 40 subjects were randomized to the Treatment Phase and received at least one dose of study drug, thereby comprising the Treatment Phase Safety Set. Thirty-seven subjects (92.5%) completed all five treatment periods and were included in the Treatment Phase Pharmacodynamic Set. None of the subjects had protocol deviations or other circumstances that could exclude them from analysis; therefore, 37 subjects were included in the Treatment Phase Per Protocol Set. This sample size was considered adequate to determine an increase in drug liking at the time it was discussed with the Agency.

### 9.2.3 Demographic and Other Baseline Characteristics

For the Main Study Safety Set, all subjects reported prior opioid experience within the last 12 months. None of the subjects was opioid-dependent based on results of the naloxone challenge. Subjects also reported previous experience with cannabinoids (n = 38), stimulants (n = 20), hallucinogens (n = 14), benzodiazepines (n = 9), and a muscle relaxant (n = 1). Most subjects were male (80.0%), White (85.0%), and not Hispanic or Latino (90.0%). Subjects had a mean age of 30.3 years, ranging from 19 to 49 years.

### 9.2.4 Pharmacodynamic Results

Overall, results from Study 007 demonstrated no evidence of increased drug liking with CL-108 when compared with matched doses of hydrocodone/acetaminophen (Figure 23), confirming that the inclusion of promethazine in CL-108 did not increase drug liking. Both supratherapeutic doses (three and five times the therapeutic dose) demonstrated no statistically significant differences between CL-108 and control for drug liking.

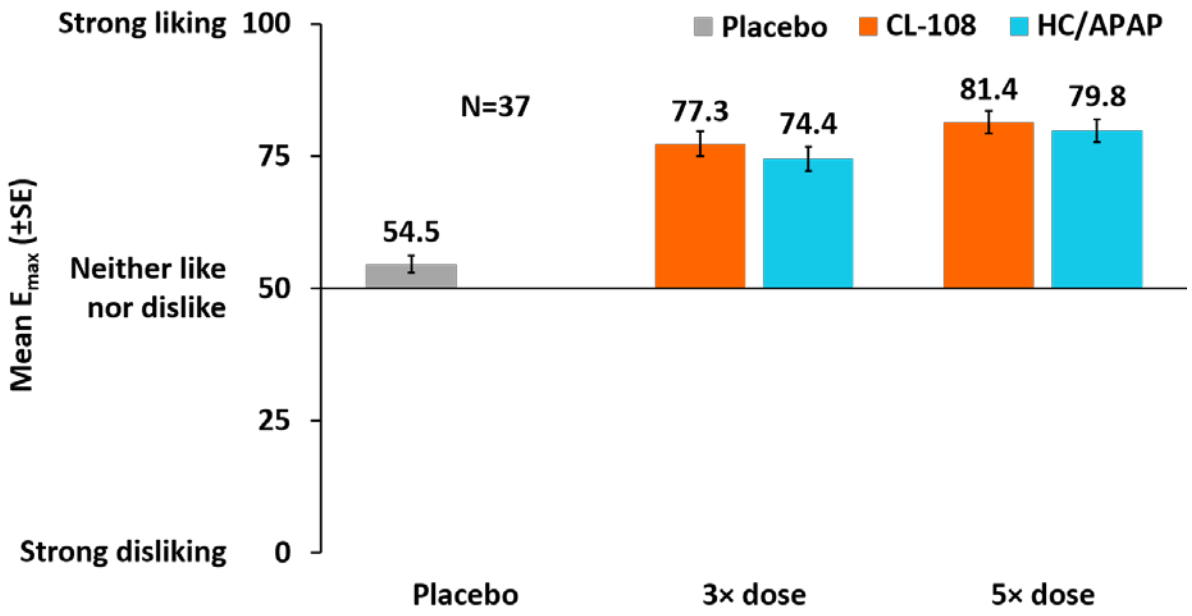


**Figure 23 No Significant Increase in Drug Liking with CL-108 Versus Hydrocodone/ Acetaminophen at Supratherapeutic Doses – Study 007**

Abbreviations: APAP, acetaminophen; CSR, clinical study report; $E_{max}$, maximum effect; HC, hydrocodone; SE, standard error.
p = 0.4737 CL-108 vs HC/APAP (5x dose), p = 0.2344 CL-108 vs HC/APAP (3x dose).
Source: 007 CSR, Tables 9 and 10.

Mean drug liking VAS scores over time are illustrated in Figure 24. All of the active treatments (CL-108 and hydrocodone/acetaminophen) showed a similar time course profile.

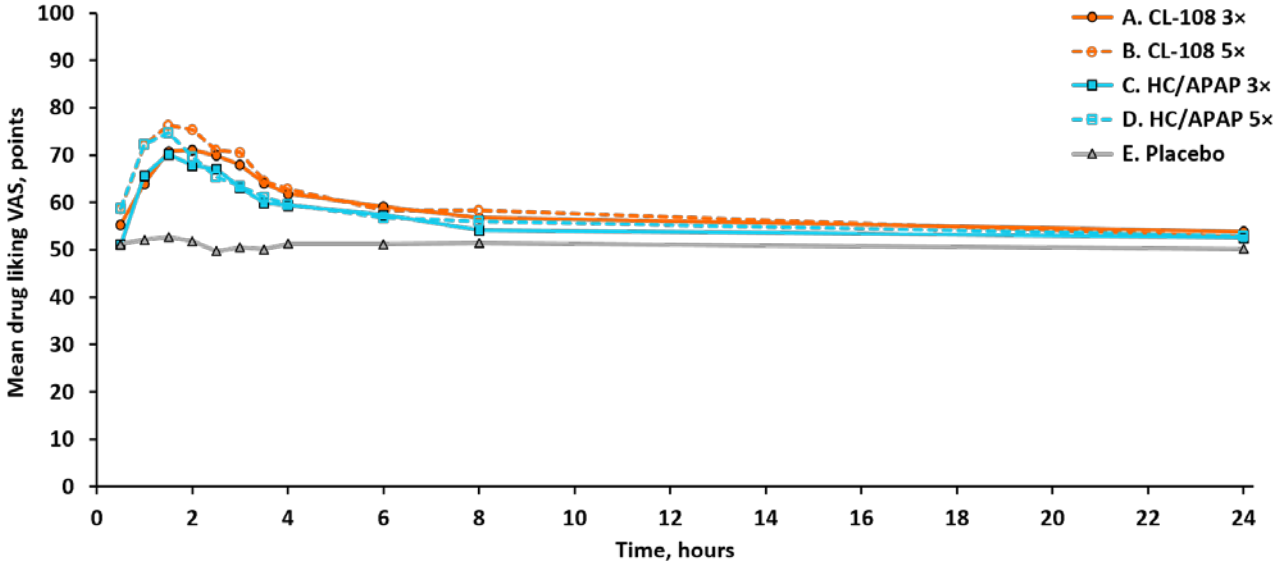


**Figure 24 Mean Scores Over Time for Drug Liking VAS – Study 007**

Abbreviations: APAP, acetaminophen; CSR, clinical study report; HC, hydrocodone; VAS, visual analog scale.
Source: 007 CSR, Figure 3.

There were also no statistically significant differences between treatment groups with regard to the important secondary endpoint, take drug again (Figure 25), high (Figure 26), and the other secondary measures, including overall drug liking, good effects, bad effects, and any effects (Table 28).

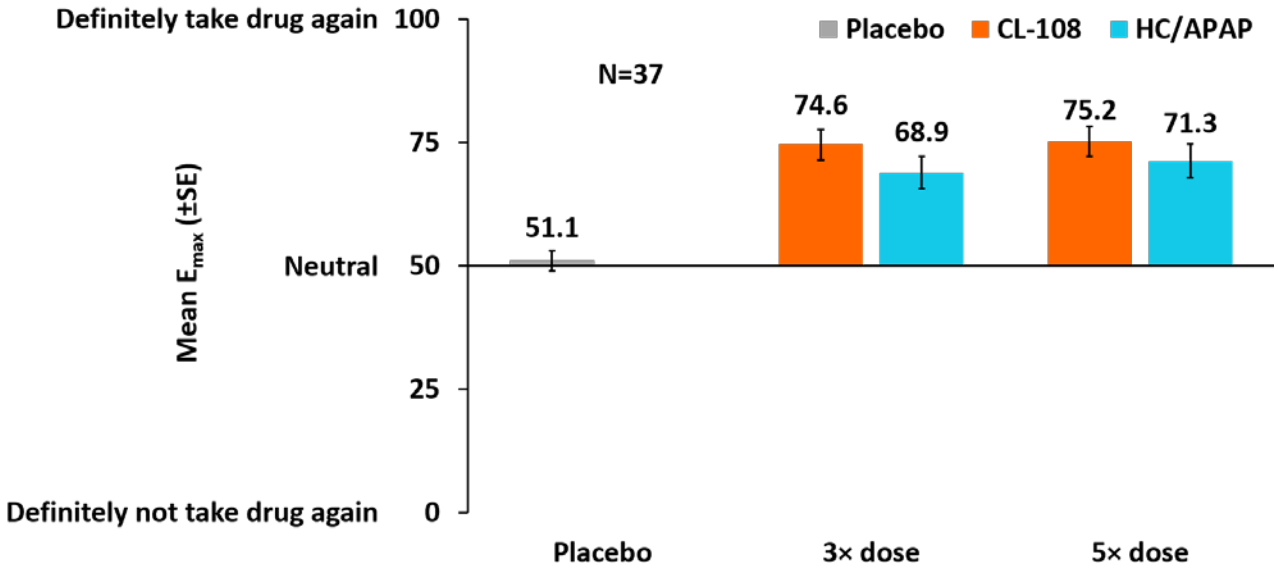


**Figure 25 No Significant Differences in Take Drug Again – Study 007**

Abbreviations: APAP, acetaminophen; CSR, clinical study report; $E_{max}$, maximum effect; HC, hydrocodone; SE, standard error.
p = 0.2877 CL-108 vs HC/APAP (5x dose), p = 0.0858 CL-108 vs HC/APAP (3x dose).
Source: 007 CSR, Tables 11 and 12.

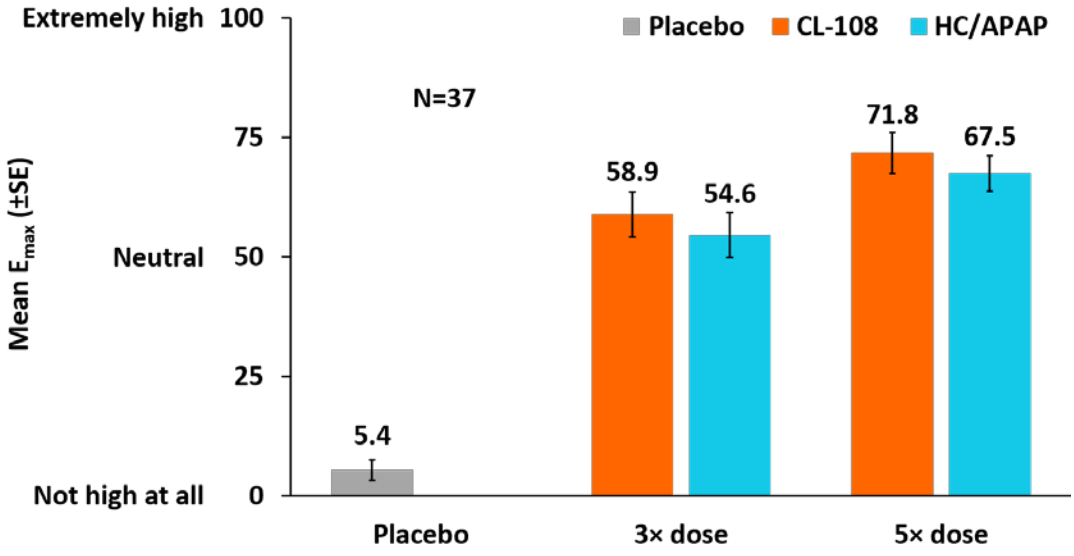


**Figure 26 No Significant Differences in High – Study 007**

Abbreviations: APAP, acetaminophen; CSR, clinical study report; $E_{max}$, maximum effect; HC, hydrocodone; SE, standard error.
p = 0.3184 CL-108 vs HC/APAP (5x dose), p = 0.4025 CL-108 vs HC/APAP (3x dose).
Source: 007 CSR, Tables 13 and 14.

**Table 28 Other Secondary Effectiveness Measures – Study 007**

| Mean (SD) $E_{max}$ | | Low Dose (3x Dose) | | High Dose (5x Dose) | |
|---|---|---|---|---|---|
| | Placebo (N = 37) | CL-108 (N = 37) | HC/APAP (N = 37) | CL-108 (N = 37) | HC/APAP (N = 37) |
| Overall Drug Liking VAS | | 70.4 (17.77) | 65.2 (17.89) | 75.8 (17.16) | 65.2 (17.89) |
| p value (CL-108 vs HC/APAP) | 52.2 (8.74) | 0.1267 | | 0.1767 | |
| Good Effects VAS | — | 59.3 (29.42) | 52.5 (29.35) | 68.3 (25.99) | 52.5 (29.35) |
| p value (CL-108 vs HC/APAP) | 6.3 (15.06) | 0.1839 | | 0.1751 | |
| Bad Effects VAS | — | 14.8 (21.89) | 20.1 (20.61) | 30.1 (29.35) | 20.1 (20.61) |
| p value (CL-108 vs HC/APAP) | 2.4 (9.68) | 0.2223 | | 0.1638 | |
| Alertness/Drowsiness VAS | — | 25.3 (18.27) | 33.3 (17.46) | 20.2 (16.44) | 33.3 (17.46) |
| p value (CL-108 vs HC/APAP) | 47.9 (15.69) | 0.0014 | | 0.0080 | |
| Any Effects VAS | — | 62.4 (26.02) | 55.4 (27.11) | 71.9 (25.85) | 55.4 (27.11) |
| p value (CL-108 vs HC/APAP) | 7.4 (15.98) | 0.0630 | | 0.4436 | |

Abbreviations: APAP, acetaminophen; CSR, clinical study report; $E_{max}$, maximum effect; HC, hydrocodone; SD, standard deviation; VAS, visual analog scale.
Source: 007 CSR, In-Text Tables 11, 12, 13, 14, 15, 16, 17, 18, and 19.

Although both supratherapeutic doses of CL-108 and hydrocodone/acetaminophen appeared to be associated with greater sedation, as measured by the alertness/drowsiness VAS, and a greater reduction in pupil diameter, sedation was greater with CL-108 (Table 28). Subjects taking the higher supratherapeutic dose also showed a slightly greater number of errors and increased response time, in a Choice Reaction Time test, which measures mental speed and processing. These results did not appear to affect drug liking, but, as a safety topic, they are addressed in the proposed warnings and precautions for CL-108.

### 9.2.5 Treatment-Emergent Adverse Events

#### 9.2.5.1 Overall Summary of TEAEs

In general, all treatments were well tolerated in this study with most TEAEs being mild in severity and consistent with the known pharmacology of opioids (e.g., pruritus, euphoria) and promethazine (e.g., sedation). There were no deaths, SAEs, or severe AEs following treatment during the study. Two subjects were withdrawn due to TEAEs; one subject was withdrawn during the Qualification Phase after experiencing dysuria considered mild and unrelated to study drug, and one subject was withdrawn during the Treatment Phase after experiencing irritability considered moderate and probably related to study drug (Table 29).

**Table 29 Summary of Adverse Events Occurring in the Dose Selection Phase and Main Study – Study 007**

| Parameter | Dose Selection Phase (N = 12) | Treatment Phase (N = 40) |
|---|---|---|
| Total number of AEs | 16 | 341 |
| Total number of subjects with at least 1 AE, n (%) | 5 (41.7) | 37 (92.5) |
| Total number of TEAEs | 14 | 338 |
| Total number of subjects with at least 1 TEAE, n (%) | 5 (41.7) | 37 (92.5) |
| Number of subjects with SAEs | 0 | 0 |
| Number of subjects with AEs leading to study drug discontinuation | 0 | 1 (2.5) |

Abbreviations: AE, adverse event; CSR, clinical study report; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Source: 007 CSR, Table 23.

### 9.2.5.2 Frequently Reported TEAEs

During the Treatment Phase, the most commonly reported TEAEs were pruritus, euphoric mood, somnolence, and headache (Table 30). Incidences of these TEAEs increased with increasing dose of study drug, except for reports of euphoric mood and headache with hydrocodone/ acetaminophen, which were similar at both doses.

The incidence of nausea was lower after administration of CL-108 than with comparable doses of hydrocodone/acetaminophen (Table 30). One subject experienced nausea after administration of placebo. The incidence of nausea increased with increasing dose of either CL-108 or hydrocodone/acetaminophen. No vomiting occurred after administration of CL-108 or placebo; however, four subjects experienced vomiting after administration of hydrocodone/acetaminophen.

**Table 30 TEAEs in ≥ 5% of Subjects by Treatment at Onset (Main Study; Safety Set, N = 40) – Study 007**

| Preferred Term | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Placebo (N = 39) | CL-108 | | HC/APAP | |
| | | Low Dose (N = 40) | High Dose (N = 39) | Low Dose (N = 38) | High Dose (N = 39) |
| Total subjects with any TEAE | 14 (35.9) | 30 (75.0) | 34 (87.2) | 28 (73.7) | 31 (79.5) |
| Pruritus | 1 (2.6) | 13 (32.5) | 23 (59.0) | 14 (36.8) | 17 (43.6) |
| Euphoric mood | 0 | 10 (25.0) | 13 (33.3) | 10 (26.3) | 9 (23.1) |
| Somnolence | 0 | 7 (17.5) | 11 (28.2) | 4 (10.5) | 9 (23.1) |
| Headache | 3 (7.7) | 3 (7.5) | 5 (12.8) | 6 (15.8) | 7 (17.9) |
| Irritability | 1 (2.6) | 1 (2.5) | 5 (12.8) | 2 (5.3) | 3 (7.7) |
| Pruritus generalized | 0 | 4 (10.0) | 2 (5.1) | 4 (10.5) | 4 (10.3) |
| Constipation | 5 (12.8) | 3 (7.5) | 2 (5.1) | 2 (5.3) | 3 (7.7) |
| Feeling hot | 1 (2.6) | 2 (5.0) | 3 (7.7) | 2 (5.3) | 2 (5.1) |
| Nausea | 1 (2.6) | 1 (2.5) | 3 (7.7) | 3 (7.9) | 7 (17.9) |
| Dizziness | 0 | 1 (2.5) | 2 (5.1) | 1 (2.6) | 1 (2.6) |
| Disturbance in attention | 0 | 1 (2.5) | 2 (5.1) | 0 | 0 |

| Preferred Term | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Placebo (N = 39) | CL-108 | | HC/APAP | |
| | | Low Dose (N = 40) | High Dose (N = 39) | Low Dose (N = 38) | High Dose (N = 39) |
| Vision blurred | 0 | 1 (2.5) | 2 (5.1) | 2 (5.3) | 1 (2.6) |
| Hiccups | 0 | 2 (5.0) | 1 (2.6) | 0 | 0 |
| Abdominal pain upper | 0 | 1 (2.5) | 1 (2.6) | 2 (5.3) | 2 (5.1) |
| Bruxism | 1 (2.6) | 1 (2.5) | 1 (2.6) | 2 (5.3) | 2 (5.1) |
| Abnormal dreams | 2 (5.1) | 1 (2.5) | 1 (2.6) | 1 (2.6) | 0 |
| Dysgeusia | 0 | 2 (5.0) | 0 | 1 (2.6) | 1 (2.6) |
| Feeling of relaxation | 0 | 2 (5.0) | 0 | 0 | 0 |
| Back pain | 2 (5.1) | 0 | 2 (5.1) | 0 | 0 |
| Anxiety | 0 | 0 | 1 (2.6) | 0 | 3 (7.7) |
| Hot flush | 0 | 0 | 1 (2.6) | 0 | 2 (5.1) |
| Vomiting | 0 | 0 | 0 | 1 (2.6) | 3 (7.7) |
| Dyspepsia | 2 (5.1) | 0 | 0 | 0 | 1 (2.6) |

Abbreviations: APAP, acetaminophen; CSR, clinical study report; HC, hydrocodone; TEAE, treatment-emergent adverse event.
Source: 007 CSR, In-Text Table 26.

At the supratherapeutic doses studied, AEs potentially related to cognitive impairment included disturbance in attention (1 [2.5%] subject treated with the low supratherapeutic dose of CL-108 and 2 [5.1%] subjects treated with high-dose CL-108) and speech disorder (1 [2.5%] subject treated with low-dose CL-108). Disturbance in attention and speech disorder were not reported with hydrocodone/acetaminophen or placebo.

There were no AEs of hypotension, seizures, or convulsions in this study, even at the three- and five-times supratherapeutic doses of CL-108.

#### 9.2.5.3 Deaths and Other Serious Adverse Events

No deaths or other SAEs were reported during this study.

#### 9.2.5.4 TEAEs Resulting in Discontinuation of Study Drug

One subject had TEAEs (irritability) that resulted in discontinuation of study drug. The subject first experienced irritability approximately three hours after administration of high-dose CL-108 in Period 3 (considered mild, constant, and probably related to study drug); this TEAE resolved after approximately 4.5 hours. The subject experienced a second TEAE of irritability (considered moderate, intermittent, and probably related to study drug) approximately 2.5 days after the first TEAE was resolved, with onset approximately 10 minutes before receiving the high-dose hydrocodone/acetaminophen treatment; this TEAE resolved approximately 24 hours later. The subject was withdrawn the day following the administration of this particular treatment.

### 9.3 Tablet Usage and Returns in Phase 3 Trials

In addition to the HAL study, Charleston also evaluated how patients used CL-108 in the clinical trial program. In each of the Phase 3 studies, very few capsules/tablets of CL-108 were

unaccounted for (Table 31). More than 99% of the dispensed capsules/tablets were accounted for across the Phase 3 trials.

**Table 31 CL-108 Investigational Product Accountability in Phase 3 Studies**

| Study Number | Number of Patients Randomized | Number of Capsules/Tablets Dispensed | Number (%) of Capsules/Tablets Lost/Unaccounted |
|---|---|---|---|
| 002 | 211 | 6,002 capsules | 24 (0.40%) |
| 003 | 252 | 7,560 capsules | 26 (0.34%) |
| 006 | 179 | 16,110 tablets | 173 (1.07%) |

## 9.4 Abuse Potential and Human Abuse Liability Conclusions

Reports suggest that promethazine and other antihistamines can be abused in combination with opioids, but there is limited evidence that promethazine potentiates the high associated with opioids or that combinations of promethazine with opioids represents a substantial public health concern. No increased risk of abuse was observed in the extensive clinical program of CL-108 and the analyses conducted to evaluate the abuse potential. In evaluating the PK of hydrocodone in Study 012, the abuse quotient ($C_{max}$ divided by $T_{max}$) was lower for CL-108 than for Norco (12.9 vs 17.2) in healthy subjects (as described in Section 5.1.2.2). Additionally, the discrepancy of unaccounted CL-108 capsules/tablets in the clinical program was minimal. Finally, the results from the HAL study, even at supratherapeutic doses, indicated that the addition of promethazine to the combination of hydrocodone and acetaminophen results in no greater abuse potential than what is typically observed with a product containing hydrocodone and acetaminophen in the same dosages or other IR opioid-combination products.

# 10.0 RISK MITIGATION AND RESPONSIBLE USE

While no increase in abuse potential was observed with CL-108 in the clinical program, Charleston recognizes the public health implications of opioids, specifically IR opioids, and is committed to the national movement to address the opioid abuse crisis. Regulators, manufacturers, and the medical community need to implement a multifaceted approach. Charleston is committed to fostering responsible prescribing and safe use of CL-108 and will implement a comprehensive abuse mitigation program through labeling, packaging, and commercialization. This program intends to reduce the availability and quantity of CL-108 by limiting the dose and duration of use, and by putting mechanisms in place to facilitate the return of unused CL-108 tablets.

## 10.1 Labeling

We agree with the FDA and Dr. Gottlieb regarding the need for new strategies to address the crisis of opioid addiction through innovation in packaging, storage, and disposal and that the medical community should limit the quantity of opioid analgesics being prescribed for acute pain. To achieve this objective, Charleston has taken two important steps. First, short-term use for acute pain (generally less than 14 days) has been defined and is stated both in the proposed label and patient medication guide. Second, we have proposed a dosing schedule of one tablet every 4- to 6-hours as needed, for a maximum daily dosage of six tablets. This is a departure from the current practice of IR hydrocodone/acetaminophen combination prescribing, which is one to two tablets every 4- to 6-hours as needed.[17] Patients can be instructed to take a total of up to 12 tablets per day (limited to 12 tablets based on acetaminophen maximum dose), often for durations longer than 14 days.

## 10.2 Packaging

To further moderate dosing and reduce the potential availability of unused product, Charleston is proposing limited-duration 3-, 5-, and 7-day packaging, utilizing an F1/Child Resistant Container Closure System (carton) for securing blistered tablets, with a total of 18, 30, and 42 tablets, respectively (Figure 27). We believe this approach will help address the direction from FDA and state representatives to reduce the size of opioid prescriptions for acute pain, and aligns with both the literature regarding the optimal duration of opioid therapy in this setting[19] (as described in Section 2.1) and our experience in the Phase 3 clinical program (Table 32). Charleston is also collaborating with a third-party company to develop a buy-back program in order to facilitate return of unused CL-108 tablets from patients for appropriate disposal.


**Figure 27 Draft CL-108 3-, 5-, and 7-Day Packaging (F1/Child Resistant Container Closure System)**

**Table 32 Exposure in Phase 3 Studies Supporting Proposed CL-108 Packaging**

| | Cumulative Dose of CL-108 by Study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Study 002 | | | Study 003 | | | Study 006 | | |
| | Mean | Median | Maximum | Mean | Median | Maximum | Mean | Median | Maximum |
| | 12.7 | 13.0 | 28 | 17.5 | 17.0 | 27 | 30.0 | 24.0 | 90 |
| Proposed Packaging | 3-day 18 tablets | | 5-day 30 tablets | 3-day 18 tablets | | 5-day 30 tablets | 5-day 30 tablets | | 7-day[a] 42 tablets |

[a] All patients enrolled in Study 006 were given 90 tablets for 14 therapy days for an average of six tablets per day over seven days or 42 tablets.

## 10.3 Other Risk Mitigation Strategies

In addition to labeling and limited-duration packaging, Charleston is taking a responsible commercialization approach.

- *Distribution*—A third-party logistics company with extensive Schedule II opioid analgesics experience will be involved throughout the supply chain. They will report any suspicious ordering, dispensing, and distribution activities to Charleston's executive team and the appropriate authorities.
- *Training*—Charleston will train all customer-facing personnel on best practices in acute pain, addiction medicine, OINV, and the appropriate use of CL-108. Our representatives will also be trained to recognize and report any suspicious activity appropriately.
- *Monitoring and surveillance*—Charleston will employ a variety of known methods such as the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System, surveys, chart reviews, media and other known active and passive surveillance systems for ongoing monitoring and will track patient experience and use, physician prescribing patterns, and trends in pharmacy ordering and dispensing.
- *Pharmacovigilance*—A pharmacovigilance plan will utilize an ARGUS database to provide ongoing safety monitoring and reporting to the FDA and other stakeholders.
- *Risk Evaluation and Mitigation Strategy (REMS)*—The FDA has announced that a class-wide REMS will be implemented for IR opioids, which is expected to focus on prescriber and patient education. Charleston will collaborate with other IR opioid manufacturers to develop recommendations for the REMS and will comply fully with its terms.

The distribution, training, monitoring and surveillance, and pharmacovigilance plans will be reviewed periodically by Charleston's Independent Risk Management Safety Advisory Board.

## 10.4 Risk Mitigation and Responsible Use Conclusions

Charleston plans to conduct appropriate distribution, monitoring, surveillance, and pharmacovigilance programs, and will work with the Agency on the class-wide REMS for IR opioids. Charleston agrees with the Agency that the medical community must find ways to reduce the abuse, misuse, and diversion of analgesics, and will use the tools described above and future innovations to provide CL-108 for patients with acute pain in the most prudent ways possible.

# 11.0 BENEFIT-RISK SUMMARY

OINV is one of the most burdensome adverse effects of short-term opioid administration and has significant adverse effects on patient recovery, clinical outcomes, and healthcare costs. The lack of approved medications to safely and effectively treat acute pain and OINV places a significant burden on patients and interferes with pain management.[8,86-88] Therefore, a need exists for effective short-term management of acute pain while also preventing and reducing OINV. To address this patient need, Charleston developed CL-108, a novel opioid-antiemetic product containing hydrocodone (7.5 mg) and acetaminophen (325 mg) for pain relief and a unique rapid-release low-dose (12.5 mg) promethazine for OINV prevention and reduction.

## 11.1 Benefits of CL-108

The efficacy of CL-108 was thoroughly investigated both in terms of pain relief and OINV as co-primary endpoints in two pivotal Phase 3 studies (Studies 002 and 003) that used different but complementary and well-established pain models (post-molar extraction pain and post-bunionectomy pain).

Overall, both pivotal efficacy studies met their co-primary endpoints for analgesia and OINV, and consistent efficacy was demonstrated across key secondary endpoints. CL-108 provided significant pain relief compared with placebo and a significant reduction in the risk of developing OINV compared with active-control (Norco).

- CL-108 provided significant relief of moderate-to-severe pain compared to placebo in both studies (both $p < 0.001$). Consistent with the primary analgesic endpoints, significant evidence of pain relief was demonstrated by CL-108 compared to placebo for secondary analgesic endpoints, including total pain relief and the percentage of maximum total pain relief, clinically meaningful relief, affective and sensory qualities of pain, and the PGE. Enhanced analgesia compared to Norco was also observed, likely as a result of the effect of CL-108 on OINV.
- The incidence of OINV (two-component definition [occurrence of any vomiting or use of any rescue antiemetic]) was reduced by 64% relative to Norco in Study 002 and by 74% in Study 003. In addition to a reduction in the incidence of OINV, outcomes such as the frequency of retching and vomiting, the occurrence and severity of nausea, and the use of antiemetics were significantly reduced following CL-108 treatment compared with Norco in both studies. Significantly more patients using CL-108 in both studies also reported no nausea, vomiting, or use of antiemetic (complete response) than patients using Norco. An exploratory analysis showed preventing and reducing OINV improves acute pain management.

The efficacy of CL-108 demonstrated in the pivotal Phase 3 trials was further supported by the effectiveness of CL-108 for joint pain and stiffness and improvements in activities of daily living observed in the Phase 3, actual-use safety study (Study 006) in patients with moderate-to-severe acute pain (flare) associated with osteoarthritis of the knee or hip.

Clinical evidence from these studies confirms that CL-108 met its treatment goals of managing pain while preventing and reducing OINV.

## 11.2 Risks of CL-108

The safety of CL-108 was also thoroughly evaluated in the clinical program and was based primarily on data from the pivotal efficacy and safety studies (Studies 002 and 003), the open-label, Phase 3 actual-use safety study (Study 006), and the HAL study (Study 007). Data from these studies are supplemented by safety findings for the RLDs, namely Vicoprofen, Ultracet, and Phenergan. In the pivotal trials, nausea and vomiting was an efficacy endpoint, and the nine other expected opioid-related side effects were documented by active surveillance through the OSS (a questionnaire of AEs adapted from the SDS and rated on Likert scales) at protocol-defined time points. Patient reports of other AEs were also collected (in a spontaneous, nondirected manner) daily in these studies. In the actual-use, safety study, patients spontaneously reported any AEs daily in a diary.

CL-108 demonstrated a consistent safety profile across the pivotal and actual-use safety studies. In the pivotal studies, opioid-related side effects of drowsiness, confusion, difficulty concentrating, and dry mouth were reported more frequently in the CL-108 group than in the Norco group. Drowsiness was the most commonly reported side effect in all treatment groups, which was not unexpected given that hydrocodone and promethazine are known to be associated with increased drowsiness. Most patients reported mild to moderate opioid-related symptoms, and the severity of drowsiness decreased over the five-day observation period. Opioid-related symptoms were dose related, as higher rates were observed when patients took five or six tablets per day, which is higher than the mean daily dose of three tablets taken over the five-day treatment observation periods and higher than when dosing was as needed (approximately two tablets per day). Furthermore, no patient had a dose reduction or discontinued study drug because of drowsiness, and no clinical sequelae or respiratory depression were reported. The rates of spontaneously reported TEAEs were generally comparable across the treatment groups, and the majority of events were mild to moderate in intensity. The most frequent (> 1%) adverse reactions with CL-108 were abdominal pain, syncope/presyncope, and pyrexia. Although these events occurred in only a few patients, there was an increased frequency with CL-108 compared to Norco. In these studies, CL-108 did not have a significant effect on the development of other relatively rare AESIs, including respiratory depression/respiratory dyspnea, seizures, or dyskinesia.

Tolerability did not worsen with continued use of CL-108 in the safety study under conditions of actual use in which CL-108 was evaluated for as-needed use with a mean daily dose of two tablets per day. Based on data from these studies, the safety and tolerability risks identified for CL-108 were as expected based on the components of CL-108 and the known safety risks for RLDs, and no new safety signal was identified.

In addition, results from the HAL study substantiated that, despite the addition of promethazine, the abuse liability potential of CL-108 (administered at supratherapeutic doses) does not differ from currently marketed hydrocodone/acetaminophen products based on overall drug liking, taking drug again, and high.

## 11.3 Overall Conclusions

A significant need remains for a single approach to address both short-term management of acute pain when an opioid is required and the prevention and reduction of OINV. At the same time, there is a need to foster new and more effective measures to address the opioid abuse crisis. Although

the available epidemiologic evidence is limited with regard to the prevalence of abuse, promethazine and other antihistamines can be abused in combination with opioids.

To address these needs, Charleston's CL-108 clinical development program replicated evidence of the safe and effective use of CL-108 to relieve pain and to prevent OINV. A significant increase in drug liking, take drug again, or high was not observed with supratherapeutic doses (three and five times the recommended dose) of CL-108 compared to the same doses of hydrocodone/ acetaminophen in the HAL study. Charleston is committed to fostering responsible use of CL-108 in the acute care setting by reducing the likelihood of abuse, misuse, and diversion through a comprehensive abuse mitigation program. This program includes appropriate labeling for short-term use (generally less than 14 days), limited dosing and duration packaging (in 3-, 5-, and 7-day packaging with an F1/Child Resistant Container Closure System), a planned buy-back program of unused CL-108 tablets, and, when enacted, participation in the class-wide REMS for IR opioids. Finally, the CL-108 label will carry the same black box warning, regarding its potential for abuse, misuse, and diversion, as with all opioids and the safety information will be consistent with the RLDs. The efficacy and safety data from the clinical development program combined with a comprehensive abuse mitigation program, as well as the Agency's previous safety findings for the RLDs of CL-108, support a favorable benefit-risk assessment for CL-108.

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