

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213426Orig1s000**

**CLINICAL REVIEW(S)**

Clinical Review  
NDA 213426  
E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

### CLINICAL REVIEW

|                                                                |                                                                                                                                             |
|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                                        | New Drug Application                                                                                                                        |
| <b>Application Number(s)</b>                                   | 213426                                                                                                                                      |
| <b>Priority or Standard</b>                                    | Standard                                                                                                                                    |
| <b>Submit Date(s)</b>                                          | May 15, 2019                                                                                                                                |
| <b>Received Date(s)</b>                                        | May 15, 2019                                                                                                                                |
| <b>PDUFA Goal Date</b>                                         | June 15, 2020(Initial PDUFA date of March 15, 2020 was extended 3 months due to major amendment submitted on March 2, 2020)                 |
| <b>Division/Office</b>                                         | DAAAP/OND                                                                                                                                   |
| <b>Reviewer Name(s)</b>                                        | Sepideh Haghpanah, M.D.<br>Yan Zhou, Ph.D.                                                                                                  |
| <b>Review Completion Date</b>                                  | March 13, 2020                                                                                                                              |
| <b>Established/Proper Name</b>                                 | Celecoxib and Tramadol Hydrochloride, Tablet                                                                                                |
| <b>(Proposed) Trade Name</b>                                   | To Be Determined                                                                                                                            |
| <b>Applicant</b>                                               | Esteve Pharmaceuticals, S.A.                                                                                                                |
| <b>Dosage Form(s)</b>                                          | Tablets: tramadol hydrochloride 44 mg and celecoxib 56 mg                                                                                   |
| <b>Applicant Proposed Dosing Regimen(s)</b>                    | 2 tablets (2 x 100 mg with 88 mg of tramadol and 112 mg of celecoxib) every 12 hours as needed for pain relief                              |
| <b>Applicant Proposed Indication(s)/Population(s)</b>          | Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate |
| <b>Recommendation on Regulatory Action</b>                     | Complete Response                                                                                                                           |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b> | Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate |

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## Glossary

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|                  |                                                 |
|------------------|-------------------------------------------------|
| ADaM             | analysis dataset model                          |
| ADL              | activities of daily living                      |
| AE               | adverse event                                   |
| ANCOVA           | analysis of covariance                          |
| ANOVA            | analysis of variance                            |
| AUC              | area under the concentration-time curve         |
| BA               | bioavailability                                 |
| BID              | twice daily                                     |
| BMI              | body mass index                                 |
| BOCF             | baseline observation carried forward            |
| C <sub>max</sub> | maximum serum concentration                     |
| CNS              | central nervous system                          |
| COX-2            | cyclooxygenase-2 (selective inhibitor)          |
| ECG              | electrocardiogram                               |
| ER/LA            | extended-release and long-acting                |
| FA               | full analysis (set)                             |
| FDA              | Food and Drug Administration                    |
| GCP              | good clinical practice                          |
| IASP             | International Association for the Study of Pain |
| IND              | investigational new drug                        |
| iPSP             | Initial Pediatric Study Plan                    |
| IR               | immediate release                               |
| LOCF             | last observation carried forward                |
| LS               | least squares                                   |
| MI               | multiple imputation                             |
| MRL              | Mundipharma Research Ltd                        |
| NDA              | new drug application                            |
| NPRS             | Numerical Pain Rating Scale                     |
| NSAID            | nonsteroidal anti-inflammatory drug             |
| PAR              | pain relief                                     |
| PI               | pain intensity                                  |
| PID              | pain intensity difference                       |
| PP               | per protocol                                    |
| PT               | preferred term                                  |
| QID              | four times daily                                |
| QOL              | quality of life                                 |
| RLD              | reference listed drug                           |
| REMS             | risk evaluation and mitigation strategy         |

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|        |                                   |
|--------|-----------------------------------|
| SA     | safety analysis (set)             |
| SAE    | serious adverse event             |
| SPID   | sum of pain intensity difference  |
| SOC    | system organ class                |
| TEAE   | treatment-emergent adverse event  |
| TOTPAR | total pain relief                 |
| VAS    | visual analog scale               |
| WOCF   | worst observation carried forward |

## 1. Executive Summary

---

### 1.1. Product Introduction

The Applicant has developed [TRADENAME, E-58425], celecoxib and tramadol, tablet, as a fixed-dose drug-drug combination product for the proposed indication of management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. One 100 mg tablet of celecoxib and tramadol contains 56 mg of celecoxib and 44 mg of tramadol hydrochloride, with a molecular ratio of 1:1 and a weight ratio of 1.27:1 for celecoxib and tramadol. The proposed dosing regimen is two tablets (celecoxib 112 mg and tramadol 88 mg) every 12 hours as needed for pain relief (PAR). The Applicant's goal was to develop a formulation of two analgesics of different classes such that the recommended dose of each component of the drug is less than the recommended dose of each component when taken individually for management of acute pain.

The Applicant submitted a 505(b)(2) application that relies in part on FDA's findings of safety and efficacy for Celebrex® (celecoxib) and Ultram® (tramadol hydrochloride or tramadol) as individual components. Celecoxib and tramadol are analgesic medications with different mechanisms of action. Celecoxib is a cyclooxygenase-2 (COX-2) selective inhibitor in the class of nonsteroidal anti-inflammatory drugs (NSAIDs). Tramadol is a  $\mu$ -opioid agonist and a norepinephrine and serotonin re-uptake inhibitor. Celecoxib products and tramadol products have been widely marketed and used for treatment of pain since the times of their approval. At the time of this review, there are no approved products containing combinations of tramadol and celecoxib in or outside the United States.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of NDA 213426 for [TRADENAME, E-58425], celecoxib and tramadol, tablet, for the proposed indication.

The Applicant performed five Phase 1 bioavailability (BA) studies (ESTEVE-SACO4-103, ESTEVE-SACO4-102, ESTEVE-SACO4-104, ESTEVE-SACO4-105, and ESTEVE-SUSA-101). The BA of celecoxib and tramadol in [TRADENAME, E-58425] support bridging to the previous findings of safety and efficacy for Celebrex and Ultram.

The Applicant performed one Phase 3 factorial study (ESTEVE-SUSA-301) that fulfilled the requirements for fixed-combination prescription drugs under 21 CFR 300.50. The Phase 3 study demonstrated that each component of E-58425 was contributing to the efficacy of the product and E-58425 had superior efficacy compared with placebo.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Integrated Assessment

The Applicant has developed E-58425, celecoxib and tramadol, tablet, as a fixed-dose drug-drug combination product for the proposed indication of management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Pain is a multifactorial medical condition that can occur in a variety of clinical settings. Acute pain is generally self-limited and requires treatment for no more than a few weeks. Untreated or poorly treated acute pain can result in patient dissatisfaction, increased cost of treatment, prolongation of hospital stays, and progression of acute pain to chronic pain. Acute pain can be a serious medical condition that can significantly impact patients' function and quality of life (QOL). Acute pain should be managed adequately and effectively to minimize suffering, morbidity, and potential long-term negative consequences.

The terms mild, moderate, or severe are often used by patients and health care providers to describe pain severity. This description provides a subjective measure of pain level and generally correlates with pain scores within the clinical context under evaluation.

Treatment of pain must be based on an individualized approach in each patient to achieve an optimal outcome. The goal of treatment is to control pain to improve physical function, activities of daily living (ADLs), social and emotional well-being, and QOL. There are multiple pharmacologic and nonpharmacologic therapeutic options available for pain. Pharmacologic treatment options for management of acute pain include multiple classes of medications such as acetaminophen, NSAIDs, anesthetics (such as lidocaine), anticonvulsants, antidepressants, opioids, and combination products (e.g., combination of opioid and acetaminophen/NSAID). Non-opioid treatment options should be considered as first line therapy for pain management unless it is clear that these options will be inadequate. Opioids or combination products that contain opioids may be necessary for treatment of moderate to severe pain for which alternative treatments are inadequate.

The proposed product is a fixed-dose combination product containing celecoxib and tramadol, analgesic medications with different mechanisms of action. Celecoxib is a COX-2 selective inhibitor in the NSAID class. Tramadol is a  $\mu$ -opioid agonist and a norepinephrine and serotonin re-uptake inhibitor. Celecoxib and tramadol have been marketed for more than 20 years with

relatively well-characterized safety profiles. At the time of this review, there are no approved products containing combinations of tramadol and celecoxib in or outside the United States.

The benefit-risk assessment of E-58425 incorporates the components described in the Agency's draft guidance *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework*, guidance for industry (June 2019). These considerations are summarized here:

A. Benefits to the Patient Using the Drug as Labeled

- The Applicant performed one Phase 3 factorial study (ESTEVE-SUSA-301) designed to fulfill the requirements for fixed-combination prescription drugs under 21 CFR 300.50 of the Federal Food, Drug and Cosmetic Act. The study was designed to demonstrate that each component of E-58425 contributes to the efficacy of the product. This study provides evidence supporting a finding of analgesic efficacy for E-58425.
- The Phase 3 study was performed in patients who had moderate to severe pain after bunionectomy. Postoperative acute pain is one of the pain models that is commonly used in clinical trials for analgesic drug development programs.

B. Risks to the Patient Using the Drug as Labeled

- E-58425 contains celecoxib and tramadol as its active ingredients. Relative BA studies of E-58425 demonstrated comparable or lower systemic exposure to celecoxib and tramadol compared with individual use of each drug within the labeled recommended dose range. The systemic safety of combination product E-5842 is expected to be comparable to the systemic safety of each individual component. Review of safety data from clinical studies of E-58425 did not reveal any novel risks.
- E-58425 is not formulated with any excipients to deter abuse or resist manipulation.
- There are no data to suggest that the drug characteristics of E-58425 increase or decrease the risk for respiratory depression, sedation, or development of opioid use disorder in patients relative to other tramadol products. Each E-58425 100 mg tablet contains 44 mg of tramadol. The proposed dosage of E-58425 is 200 mg every 12 hours, which contains tramadol 88 mg per dose with a total of 176 mg of tramadol per day. This is within the recommended maximum dose range for the reference product, Ultram, which is 200-400 mg per day.

- In the clinical studies performed by the Applicant, the most common adverse events (AEs) reported with E-58425 were comparable to those reported with tramadol, including nausea, vomiting, and somnolence and dizziness. No unexpected safety issues were reported with the use of E-58425 in clinical studies performed by the Applicant.

C. Effectiveness and Safety of the New Drug Relative to Approved Analgesics

- There are no adequate comparative efficacy data for E-58425 relative to other approved opioid or nonopioid analgesic drugs. The Phase 3 factorial study compared lower doses of the individual components of E-58425 than are optimal for treatment of acute pain and this study is not suitable for making comparative efficacy claims.
- The clinical studies performed for this NDA were designed to evaluate the primary objectives of efficacy or BA of E-58425. These studies were not designed to prospectively evaluate prespecified safety outcomes. Thus, no direct comparisons can be made regarding the comparative safety of E-58425 to other analgesics.
- E-58425 is a fixed-dose combination product dosed every 12 hours, which provides less flexibility in making dose adjustments. This may be relevant in situations where patients do not tolerate the recommended initial dose of tramadol, which is on the upper end of the recommended dose range in the Ultram label.
- There are no data to support that E-58425 has any advantage over other available approved analgesic drugs.
- There was no evidence that AEs typically associated with opioid analgesic drugs occur at a higher rate or with greater severity with E-58425.

D. Broader Public Health Effects: Risks and Mitigation of Risks Related to Misuse, Abuse, Opioid Use Disorder, Accidental Exposures, and Overdose

- The opioid epidemic, driven in part by increased prescribing, is a major public health issue. There has been concern that approval of new opioid analgesic drug products may lead to increased prescribing of opioid analgesics. However, in recent years the number of opioid analgesics dispensed has not trended in the same direction as numbers of opioid analgesic drug approvals. Examination of dispensed opioid prescriptions and opioid approvals showed a decrease in estimated annual numbers of opioid analgesics dispensed since 2010 and increasing numbers of opioid analgesic drug approvals per year since 2010 (Chai et al. 2018). While these data alone do not eliminate the overall concern, the observed trends do not support the hypothesis that new opioid analgesic approvals lead to increased prescribing of opioid analgesics.

- As of August 18, 2014, the Drug Enforcement Administration placed tramadol (including its salts, isomers, and salts of isomers) as Schedule IV under the Controlled Substances Act (79 FR 37623), applicable to all tramadol-containing products. Schedule IV drugs are considered to have a lower potential for abuse relative to the drugs or substances in Schedule III of the Controlled Substances Act, have a currently accepted medical use in treatment in the United States, and abuse of the drug may lead to limited physical dependence or psychological dependence relative to other drugs or substances in Schedule III [21 U.S.C. 812 (b) (4)].<sup>1</sup>
- Product-specific characteristics
  - E-58425 tablets are provided in oral tablet formulations. The method of delivery does not affect existing risk and does not introduce a novel risk.
  - There are no characteristics of E-58425 that would be expected to increase or decrease the risk of accidental exposure in children (e.g., tablet size, color, flavor, packaging configuration, or appearance of tablets).
  - There are no specific characteristics of E-58425 that would be expected to increase or decrease the risk of misuse, abuse, opioid use disorder, and related adverse outcomes such as overdose and infectious complications of injection compared to other opioids. However, given that E-58425 is a co-crystal containing an opioid product, the potential risks of unintended use of E-58425 should be further evaluated. Although a co-crystal is not a new single active pharmaceutical ingredient (API) and is treated as a fixed-dose combination, E-58425 contains an opioid product and requires additional evaluation to inform its benefit risk profile in the context of broader public health. Additionally, if E-58425 is misused via unintended routes, there may be risks associated with the celecoxib component of E-58425. Thus, further assessment of potential risks of E-58425 via unintended routes of administration is required to assess whether the co-crystal formulation of celecoxib and tramadol would expose the public to any additional risks.
- Summary of single-entity tramadol product postmarket data
  - The number of dispensed single-entity tramadol prescriptions gradually declined after the product was placed under Schedule IV in 2014. However, there was an increasing trend in tramadol as a percentage of the total opioid analgesic prescriptions in recent years.

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<sup>1</sup> Re-evaluation of the scheduling status of tramadol substance was not considered as part of the review of this NDA.

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- Results from national surveys and poison center calls suggest that abuse and misuse of tramadol and comparator opioid analgesics have been declining among the general U.S. population in recent years.
- Tramadol was less frequently implicated in prescription opioid misuse, abuse, and related outcomes than were hydrocodone and oxycodone, while results were mixed for tramadol's position relative to codeine and morphine.
- Notably, tramadol abuse may have increased among people with opioid use disorder. Also, tramadol-involved overdose deaths increased from 2011 to 2017. It is uncertain whether the observed increase is due to changes in use and abuse, increased surveillance, improved documentation, or other factors.
- Risks in special populations
  - The proposed patient population for E-58425 is adults. Per the agreed initial pediatric study plan, a clinical trial in adolescents ( $\geq 12$  years and  $< 17$  years of age) would be initiated upon approval of E-58425. The planned nonclinical toxicological study will provide additional data for assessment of the benefit-risk of E-58425 in adolescents.
  - Currently, no data are available to inform a benefit-risk evaluation of E-58425 in the subpopulations of patients with mental health and/or substance use disorders.

### E. Risk Management

- E-58425 is a co-crystal containing tramadol. The risks of unintended use of E-58425 are unknown. Further assessment of potential risks of E-58425 via unintended routes of administration is required to inform whether co-crystal formulation of tramadol would expose public to any additional risks.
- Tramadol is an opioid and a Schedule IV controlled substance considered to have potential for abuse. If approved, E-58425 will be subject to the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of E-58425 outweigh potential risks in the outpatient setting.

In conclusion, the recommendation of complete response from the clinical perspective is based on a single clinical deficiency. No evaluation of the potential risks associated with unintended use of E-58425, as a co-crystal containing an opioid was submitted with the original application. On February 13, 2020, the Division requested that the Applicant perform further assessment of potential risks of E-58425 via unintended routes of administration. On March 02, 2020, the Applicant submitted an amendment in response to the Division's request. At the time of this review, this amendment is under review by nonclinical team. If the amendment is adequate to resolve this deficiency, then there will be no remaining clinical deficiencies in the application.

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Refer to the product quality section of this review for the unresolved product quality deficiency.

APPEARS THIS WAY ON ORIGINAL

### Benefit-Risk Dimensions

| Dimension                        | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Conclusions and Reasons                                                                                                                                                                                                                                                                                    |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <u>Analysis of Condition</u>     | <ul style="list-style-type: none"> <li>Pain is a multifactorial medical condition that can occur in a variety of clinical settings.</li> <li>Acute pain generally requires treatment for no more than a few weeks.</li> <li>Untreated acute pain can lead not only to short-term suffering but also to the risk of progression to chronic pain.</li> <li>Acute pain can be a serious medical condition that can significantly impact patients' function and QOL.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Acute pain should be managed adequately and effectively to minimize suffering, morbidity, and potential long-term negative consequences.                                                                                                                                                                   |
| <u>Current Treatment Options</u> | <ul style="list-style-type: none"> <li>Treatment of pain must be based on an individualized approach in each patient to achieve an optimal outcome. The goal of treatment is to control pain to improve physical function, ADLs, social and emotional wellbeing, and QOL.</li> <li>Pharmacologic treatment options for management of severe acute pain include multiple classes of medications such as acetaminophen, NSAIDs, anesthetics (e.g., lidocaine), anticonvulsants, antidepressants, opioids, and combination products (e.g., combination of opioid and acetaminophen/NSAID).</li> <li>Non-opioid treatment options should be considered first line therapy for pain management unless it is clear that these options will be inadequate. Opioids or combination products that contain opioids may be necessary for treatment of moderate to severe pain for which alternative treatments are inadequate.</li> <li>Celecoxib products and tramadol products have been widely marketed and used for treatment of pain since the times of their approval. The proposed product is a combination product containing celecoxib and tramadol.</li> </ul> | Treatment of acute pain is an unmet medical need. Although there are different therapeutic options available for management of acute severe pain, achieving optimal outcomes is challenging with existing therapies due to associated safety concerns and inadequate effectiveness of available therapies. |

| Dimension                              | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><u>Benefit</u></b>                  | <ul style="list-style-type: none"> <li>The Phase 3 factorial study demonstrated statistically significant superior efficacy of E-58425 over placebo and that each component of E-58425 was contributing to the efficacy of the product for the management of acute moderate to severe pain.</li> <li>E-58425 is a combination of two established analgesics with different mechanisms of action that each contributed to the analgesic effect in a Phase 3 study.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                  | <p>The available data provide substantial evidence to support safety and efficacy of E-58425 for the proposed indication.</p>                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b><u>Risk and Risk Management</u></b> | <ul style="list-style-type: none"> <li>Review of the available safety data for E-58425 showed a comparable safety profile to that of tramadol. In the controlled Phase 3 clinical study, the most common AEs reported with E-58425 were comparable to those reported with tramadol, including Nausea and Vomiting in system organ class (SOC) Gastrointestinal disorders, and Somnolence and Dizziness in SOC Nervous system disorders.</li> <li>The safety assessment of available data did not raise new safety concerns.</li> <li>E-58425 contains tramadol, which is an opioid. Thus, E-58425 has all the risks associated with opioid medications, including abuse, misuse, addiction, and criminal diversion.</li> <li>Potential risks associated with unintended use of E-58425, as a co-crystal containing an opioid product is not known.</li> </ul> | <p>E-58425 is considered a substance with a high potential for abuse, misuse, addiction, and criminal diversion. Further assessment of potential risks of E-58425 via unintended routes of administration is required to inform whether co-crystal formulation of tramadol would expose public to any additional risks, which is under review by nonclinical team.</p> <p>If approved, E-58425 will be subject to the Opioid Analgesic REMS to ensure that the benefits of E-58425 outweigh potential risks in the outpatient setting.</p> |

## 1.4. Patient Experience Data

### Patient Experience Data Relevant to this Application (check all that apply)

|                          |                                                                                                         |                                                                                                                                    |                                           |
|--------------------------|---------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| X                        | The patient experience data that were submitted as part of the application include:                     |                                                                                                                                    | Section where discussed, if applicable    |
|                          | X                                                                                                       | Clinical outcome assessment (COA) data, such as                                                                                    |                                           |
|                          | X                                                                                                       | Patient reported outcome (PRO)                                                                                                     | Sec 7. Integrated Review of Effectiveness |
|                          | <input type="checkbox"/>                                                                                | Observer reported outcome (ObsRO)                                                                                                  |                                           |
|                          | <input type="checkbox"/>                                                                                | Clinician reported outcome (ClinRO)                                                                                                |                                           |
|                          | <input type="checkbox"/>                                                                                | Performance outcome (PerfO)                                                                                                        |                                           |
|                          | <input type="checkbox"/>                                                                                | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                           |
|                          | <input type="checkbox"/>                                                                                | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                           |
|                          | <input type="checkbox"/>                                                                                | Observational survey studies designed to capture patient experience data                                                           |                                           |
|                          | <input type="checkbox"/>                                                                                | Natural history studies                                                                                                            |                                           |
|                          | <input type="checkbox"/>                                                                                | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                           |
|                          | <input type="checkbox"/>                                                                                | Other: (Please specify)                                                                                                            |                                           |
| <input type="checkbox"/> | Patient experience data that were not submitted in the application, but were considered in this review: |                                                                                                                                    |                                           |
|                          | <input type="checkbox"/>                                                                                | Input informed from participation in meetings with patient stakeholders                                                            |                                           |
|                          | <input type="checkbox"/>                                                                                | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                           |
|                          | <input type="checkbox"/>                                                                                | Observational survey studies designed to capture patient experience data                                                           |                                           |
|                          | <input type="checkbox"/>                                                                                | Other: (Please specify)                                                                                                            |                                           |
| <input type="checkbox"/> | Patient experience data were not submitted as part of this application.                                 |                                                                                                                                    |                                           |

## **2. Therapeutic Context**

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### **2.1. Analysis of Condition**

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP 2017). Pain is a multifactorial medical condition that can occur in a variety of clinical settings such as trauma, musculoskeletal injury, nerve injury, visceral distension or inflammation, and postsurgical procedures. Acute pain can be a serious medical condition that can significantly impact patients’ function and QOL. Acute pain is generally self-limiting and requires treatment for no more than a few weeks. Untreated or poorly treated acute pain can result in patient dissatisfaction, increased cost of treatment, prolonged hospital stays, and progression of acute pain to chronic pain.

The terms mild, moderate, or severe are often used by patients and health care providers to describe pain severity. This description provides a subjective measure of pain level and generally correlates with pain scores within the clinical context under evaluation. However, severe pain following a dental extraction may not be qualitatively the same as severe pain following abdominal surgery, and each condition may need a different treatment approach.

### **2.2. Analysis of Current Treatment Options**

Treatment of pain must be based on an individualized approach in each patient to achieve an optimal outcome. The goal of treatment is to control pain to improve physical function, ADLs, social and emotional wellbeing, and QOL. There are multiple therapeutic approaches for the treatment of pain, including prescription and nonprescription medications, invasive and non-invasive medical procedures such as nerve blocks, occupational and physical therapies, and complementary and alternative therapies such as acupuncture, herbal medicine, and biofeedback.

Pharmacologic treatment options for pain control include multiple classes of medications such as acetaminophen, NSAIDs, anesthetics (such as lidocaine), anticonvulsants, antidepressants, opioids (including tramadol and tapentadol), and combination products containing different medications. Pain medications can be administered through a variety of different routes such as oral, intramuscular injection, intravenous injection, and topical/transdermal systems.

The goal of treatment is to control pain with minimal side effects from pain medication. The choice of medication for pain management should be based on the diagnosis, the mechanisms of pain, comorbidities, and a thorough benefit-risk assessment that demonstrates that the

benefits of a medication outweigh the risks. Non-opioid treatment options must be considered as the first line therapy for pain management. Opioids or combination products that contain opioids may be necessary for treatment of moderate to severe pain for which alternative treatments are inadequate.

The proposed product is a fixed-dose combination product containing celecoxib and tramadol. Celecoxib products and tramadol products have been widely marketed and used for treatment of pain since the time of their approval. At the time of this review, there are no approved products containing combinations of tramadol and celecoxib in or outside the United States.

Celecoxib was initially approved on December 31, 1998, under the brand name Celebrex (NDA 20998). Celebrex is a COX-2 selective inhibitor in the NSAID class. COX-2 inhibitors have fewer gastrointestinal adverse effects compared with other NSAIDs. Celebrex is supplied as 50 mg, 100 mg, 200 mg, and 400 mg capsules for oral use. Celebrex is indicated for osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients 2 years of age and older, ankylosing spondylitis, acute pain, and primary dysmenorrhea. The labeled dosage for Celebrex is as below:

For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Celecoxib is not available in combination with any other analgesic medication. A combination of amlodipine and celecoxib was approved on May 31, 2018, under trade name Consensi® for patients for whom treatment with amlodipine for hypertension and celecoxib for osteoarthritis are appropriate (NDA 210045, amlodipine/celecoxib 2.5 mg/200 mg, 5 mg/200 mg, or 10 mg/200 mg). There are multiple combination products containing NSAIDs (other than celecoxib) and opioids in different strengths such as hydrocodone bitartrate/ibuprofen 2.5 mg/200 mg to 10 mg/200 mg, oxycodone/aspirin 4.8 mg/325 mg, oxycodone/ibuprofen 5 mg/400 mg, codeine/aspirin/butalbital/cafeine 50 mg/325 mg/40 mg/30 mg, and aspirin/cafeine/dihydrocodeine bitartrate 356.4 mg/30 mg/16 mg.

Tramadol hydrochloride was initially approved on March 3, 1995, under the brand name Ultram (NDA 20281). The mechanism of action of tramadol is not completely known, but the analgesic effect of tramadol is believed to be due to both binding to  $\mu$ -opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Ultram is supplied as 50 mg strength scored tablets for oral use. Ultram is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The labeled dosage for Ultram is as below:

For patients not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: Start ULTRAM at 25 mg/day and titrated in 25 mg increments as separate doses every 3 days to reach

100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

After approval of Ultram, other products containing tramadol have been approved, including a combination of tramadol and acetaminophen [Ultracet (tramadol hydrochloride 37.5 mg and acetaminophen 325 mg) tablets, NDA 21123, approved in 2000] and an extended release formulation [Ultram ER (tramadol hydrochloride extended-release 100 mg, 200 mg, and 300 mg) tablets, NDA 21692, approved in 2005].

On August 18, 2014, the U.S. Drug Enforcement Administration placed all tramadol-containing products (including its salts, isomers, and salts of isomers) into Schedule IV of the Controlled Substances Act.

### **3. Regulatory Background**

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#### **3.1. U.S. Regulatory Actions and Marketing History**

On May 15, 2019, Esteve Pharmaceuticals, S.A. (Esteve, the Sponsor, or the Applicant) submitted NDA 213426 for E-58425, celecoxib and tramadol, tablet 100 mg, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, making reference to the FDA's previous findings on the safety and effectiveness of the two reference listed drugs (RLDs) (Celebrex and Ultram) as well as original studies performed by the Applicant. One 100 mg tablet of the product, celecoxib and tramadol, contains 56 mg of celecoxib and 44 mg of tramadol hydrochloride, with a 1:1 molecular ratio. The proposed indication is the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

#### **3.2. Summary of Presubmission/Submission Regulatory Activity**

The development program for this product, celecoxib and tramadol, occurred under IND 128177. On February 25, 2016, a pre-IND meeting was held between the Division and the Applicant. In the IND 128177 submission, the product, celecoxib and tramadol, is referred to as "co-crystal E-58425," "co-crystal," "E-58425," and "co-crystal tramadol celecoxib." Thus, the

terms “celecoxib and tramadol,” “tramadol and celecoxib,” “co-crystal E-58425,” “co-crystal,” “E-58425,” and “co-crystal tramadol celecoxib” are used interchangeably for the proposed product in this review.

At the time of pre-IND, the Applicant had completed four Phase 1 studies in Canada and had one ongoing Phase 2 study in Spain, using European Union comparators of tramadol “Adolonta” and celecoxib (ESTEVE-SACO4-104, ESTEVE-SACO4-102, ESTEVE-SACO4-103, ESTEVE-SACO4-105, and ESTEVE-SACO4-201). Refer to Table 1 for more information about these studies. The Applicant proposed one Phase 2 study and two Phase 3 studies. The following were discussed during the pre-IND meeting regarding the development program for E-58425:

- If the Applicant intends to submit a 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for one or more listed drugs, they must establish that such reliance is scientifically appropriate, using the NDA product approved in the United States.
- Based on the Applicant’s Phase 2 study conducted in Europe, the Division was concerned that BID dosing with E-58425 may not be appropriate as it was not supported by the time-to-rescue of 7 to 8 hours.
- Given the proposed dosing interval of BID or TID for the product, the proposed primary endpoint of the sum of pain intensity difference (SPID) (b) (4) for Phase 3 studies is not appropriate. The Division recommended that the Applicant use SPID 48 as the primary endpoint to provide evidence of efficacy over the first 48 hours of treatment.
- The requirements of the combination rule for E-58425 were discussed.
- The Division advised that one adequate and well-controlled factorial study is sufficient to support the NDA. The Division noted that the standard for comparative claims of superiority against another drug product is replicated evidence from clinical studies and thus two studies would be required to support a comparative claim.

Following the FDA’s recommendation to conduct an adequate pharmacokinetic bridge to the U.S.-marketed formulations of celecoxib and tramadol, the Applicant performed a 4-way cross-over Phase 1 study, Study ESTEVE-SUSA-101.

On July 29, 2016, the Applicant submitted IND 128177 proposing a Phase 3 study, ESTEVE-SUSA-301, a randomized, double-blind, active- (tramadol and celecoxib) and placebo-controlled study, to establish the efficacy of E-58425 for the management of moderate to severe postsurgical pain after bunionectomy. Study ESTEVE-SUSA-301 was designed as a full factorial study to fulfill the requirements of 21 CFR 300.50 for fixed-combination prescription drugs for this NDA.

The Food and Drug Administration Modernization Act includes a provision that requires sponsors planning to submit an application for a drug subject to the Pediatric Research Equity Act to submit an initial pediatric study plan (iPSP) early in the development process. The intent

of the iPSP is to identify needed pediatric studies early in development and begin planning for these studies. On November 18, 2016, the Applicant submitted an iPSP for E-58425, requesting a full waiver in all pediatric age groups. The Applicant stated that, regarding the development program of their product in Europe, the European Medicines Agency and the Paediatric Committee granted a product-specific waiver in July 2012 for all subsets of the pediatric population on the basis that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for pediatric patients (Decision number: P/0195/2012; PIP number EMEA-001279-PIP01-12). The Division did not agree with the full waiver request. On August 29, 2017, the Division approved supplement #039 for NDA 020281 that contraindicated Ultram in children younger than 12 years of age due to risk of life-threatening respiratory depression associated with use of tramadol-containing products in children. After discussing the iPSP at the Pediatric Review Committee and after multiple correspondences between the Division and the Applicant, the Division issued an "Agreed iPSP – Agreement" on August 28, 2017. The Division granted a partial waiver in pediatric age groups 0 to <12 years of age and deferred the pediatric clinical studies in adolescents (≥12 years and <17 years of age) until the FDA approves E-58425 for marketing. The strength or strengths to be used in the pediatric clinical study will depend on the results of the toxicology studies and the final agreement with the FDA on the clinical study protocol. The estimated milestone dates for all planned pediatric studies are listed below.

1. Toxicology studies in juvenile animals (preliminary dose range finding and pivotal study):

- Estimated protocols submission date: October 31, 2018
- Estimated studies initiation date: July 31, 2019
- Estimated studies completion date: August 31, 2020
- Estimated final reports submission date: September 30, 2020

Based on the results of the pivotal toxicology studies, the pediatric clinical study protocol ESTEVE-SUSA-P01 in adolescents will be submitted to the Agency with the following estimated timelines.

2. Clinical study ESTEVE-SUSA-P01 (pharmacokinetics, efficacy, and safety study):

- Estimated Protocol submission date: October 30, 2020
- Estimated study initiation date: January 31, 2021
- Estimated study completion date: January 31, 2022
- Estimated final report submission date: May 31, 2022

(b) (4)

On May 17, 2018, a pre-NDA meeting was held between the Applicant and the Division. A summary of clinical issues is listed below:

- Given that E-58425 is a combination of celecoxib and tramadol, an opioid analgesic, the Division anticipated that the application will be discussed at an Advisory Committee meeting to obtain input from outside experts and the public. The Applicant proposed to use “Co-crystal of Tramadol and Celecoxib” as the established name for the Co-crystal E-58425. The Division did not agree and recommended the established name of “(Celecoxib and tramadol) tablets.”
- The Division stated that the proposed product label should include safety information from the listed drugs and the completed clinical studies.
- A REMS will be necessary to ensure that the benefits of the drug outweigh the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Therefore, the Applicant will need to submit a proposed REMS with their application.
- The Division agreed that no abuse potential studies need to be conducted at this time for E-58425. The Applicant should document AEs associated with potential abuse and overdose for all clinical studies, including cases of lack of compliance or subjects who discontinue participation without returning the study medication.
- Given that E-58425 is a fixed-dose combination product, it may be difficult to adjust the dose in several situations. The Applicant should clearly elaborate:
  - How E-58425 will be initiated, e.g., using the Ultram label as an example, i.e., ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter, the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for PAR every 4 to 6 hours not to exceed 400 mg/day.
  - Dosing recommendations regarding special populations, e.g., patients with hepatic or renal deficiencies and the elderly.
  - Dosing recommendations regarding drug-interaction, e.g., poor metabolizers of CYP2C9, inhibitors of CYP2D6 and CYP3A4, and inducers of CYP3A4.

### 3.3. Foreign Regulatory Actions and Marketing History

At the time of this review, there are no other products containing any combinations of celecoxib and tramadol anywhere in the world.

Besides the development program of the proposed product in the United States, the Applicant started their development program outside the United States. In addition to the clinical studies that are included in this NDA submission, an independent third-party company [Mundipharma Research Ltd (MRL)] conducted one Phase 1 and two Phase 3 studies in Europe and Canada. The clinical studies performed by MRL are not part of this NDA submission except for the serious adverse events (SAEs) that occurred during MRL clinical studies with celecoxib and tramadol that are included in this NDA submission.

## 4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations

According to the Clinical Inspection Summary dated November 21, 2019, performed by the Office of Scientific Investigations, two clinical investigator sites were inspected for Study ESTEVE-SUSA-301. For both sites, no significant good clinical practice (GCP) deficiencies were observed. Based on the inspections study conduct appeared GCP-compliant, including sponsor oversight. All audited data were verifiable against source records and case report forms. The data from the sites appear reliable as reported in the NDA.

### 4.2. Product Quality

At the time of this review, the integrated quality assessment team has NOT recommended this application for approval. On January 27, 2020, the integrated quality assessment team noted that the field investigator could not complete an inspection of the (b) (4) (b) (4) manufacturing facility (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. The application is approvable from drug substance, biopharmaceutics, and drug product perspectives.

The proposed drug product from Esteve is formulated as an IR tablet containing co-crystal of celecoxib and tramadol hydrochloride. Co-crystals are crystalline materials composed of two or more different molecules in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds. Per *Regulatory Classification of Pharmaceutical Co-Crystals*, guidance for industry (February 2018), a co-crystal is not a new single API and is treated as a fixed-dose combination. The submitted data indicate that the intrinsic dissolution rate of tramadol hydrochloride is slowed while that of celecoxib is slightly accelerated (only at high pH) due to the co-crystallization when compared with the intrinsic dissolution rate of the respective single entity. The Applicant believes that these characteristics will support dosing tramadol every 12 hours instead of every 6 hours as recommended in the

approved immediate-release tramadol-containing products. The excipients used in the proposed product are typically used in an immediate-release product. The Applicant has confirmed the presence of co-crystals by various analytical methods. The Applicant has conducted clinical studies using tablets with the same core formulation as the proposed to-be-marketed product.

### **4.3. Clinical Microbiology**

Not applicable.

### **4.4. Nonclinical Pharmacology/Toxicology**

Refer to the review from nonclinical team.

### **4.5. Clinical Pharmacology**

The clinical pharmacology studies included a single-dose relative BA study, a multiple-dose relative BA study, and a food effect pharmacokinetic study of E-58425 tablets. The purpose of these three studies was to evaluate single-dose and multiple-dose relative BA of E-58425 tablets compared with the reference drugs and to evaluate food effect on E-58425 tablets.

We conclude from these studies that:

- After single dose administration, for the tramadol component of E-58425 tablets (total dose 88 mg), the maximum serum concentration ( $C_{max}$ ) was 30% lower and the area under the concentration-time curve (AUC) ( $AUC_t$  and  $AUC_{inf}$ ) was ~8% lower compared with Ultram tablets (total dose 100 mg). For the tramadol-M1 metabolite of E-58425 tablets, the  $C_{max}$  was 30% lower and the AUC ( $AUC_t$  and  $AUC_{inf}$ ) was ~12% lower compared with Ultram tablets. For the celecoxib component of E-58425 tablets (total dose 112 mg), the  $C_{max}$  was 15% lower and the  $AUC_t$  and  $AUC_{inf}$  was ~18% lower compared with Celebrex 100 mg capsules. This single dose relative BA study established the scientific bridge to the reference drugs Ultram and Celebrex for this 505(b)(2) application.
- After multiple-dose administration of E-58425 tablets, the accumulation ratio of tramadol  $C_{max}$  and  $AUC_t$  values (15th dose/1st dose) were 2.20-fold and 2.37-fold, respectively. The accumulation ratio of celecoxib  $C_{max}$  and  $AUC_t$  values (15th dose/1st dose) were 1.76-fold and 2.15-fold, respectively. After multiple dosing, the  $C_{max,ss}$  and  $AUC_{ss}$  values of tramadol and celecoxib components of E-58425 tablets were lower

than the reference drugs, Adolonta<sup>2</sup> and Celebrex. Based on pre-dose concentrations, the steady state appears to be achieved for all three analytes—tramadol, M1 metabolite, and celecoxib—of E-58425 tablets. There were no differences in the tramadol and celecoxib half-lives after multiple dosing between E-58425 tablets and the reference drugs, Adolonta and Celebrex.

- When E-58425 tablets were administered under fed conditions, the AUC, C<sub>max</sub>, and T<sub>max</sub> of the tramadol component were not significantly affected. For the celecoxib component, the T<sub>max</sub> was delayed by approximately 2.5 hours and resulted in an approximate 30% increase in C<sub>max</sub> and AUC, which was similar to the food effect described in the Celebrex label. It is reasonable to recommend that E-58425 tablets be taken without regard to food.

Refer to the review from Clinical Pharmacology team for further details.

#### **4.6. Devices and Companion Diagnostic Issues**

Not applicable.

#### **4.7. Consumer Study Reviews**

Not applicable.

### **5. Sources of Clinical Data and Review Strategy**

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#### **5.1. Table of Clinical Studies**

In this NDA submission, the Applicant included five Phase 1, one Phase 2, and one Phase 3 clinical studies, as listed in Table 1.

Phase 1 studies in healthy volunteers included one comparative BA study (single dose) using the U.S. references (ESTEVE-SUSA-101) and four studies using European references (ESTEVE-SACO4-102, ESTEVE-SACO4-103, ESTEVE-SACO4-104, and ESTEVE-SACO4-105). Study ESTEVE-SUSA-101 was used to provide BA bridging data for reliance upon FDA's finding of safety and effectiveness of the RLDs, Celebrex and Ultram.

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<sup>2</sup> The Applicant has established the required scientific bridge for this 505(b)(2) application via single-dose relative BA between E-58425 tablets and US approved reference drugs Ultram (Tramadol 50 mg tablets) and Celebrex (100 mg capsule). Adolonta (Tramadol 50 mg capsule) is not a US-approved drug. The pharmacokinetic comparison between E-58425 tablets and Adolonta capsules after multiple doses was used as supportive information and is not required to establish the scientific bridge.

Clinical Review  
NDA 213426  
E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

ESTEVE-SACO4-201 was a Phase 2 dose finding study on postsurgical acute pain after oral surgical procedures involving extraction of two (ipsilateral) or more impacted third molars requiring bone removal. This study was a placebo-controlled, single dose study that provided the first set of efficacy data for use of E-58425 in acute pain, comparing different doses of the product with a formulation of tramadol marketed in Europe and placebo.

ESTEVE-SUSA-301 was a Phase 3 full factorial study comparing E-58425 to tramadol, celecoxib, and placebo in a postsurgical acute pain model (bunionectomy with osteotomy).

Additionally, MRL performed one Phase 1 and two Phase 3 studies in Europe and Canada, using E-58425 under the name MR308, as shown in Table 2. The studies performed by MRL are not part of this NDA submission and are not included in the integrated summary of efficacy. Any SAEs that occurred in these studies are reported by the Applicant and are included in the safety review.

Clinical Review  
NDA 213426  
E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

**Table 1: Listing of Clinical Trials Conducted by the Applicant Relevant to This NDA**

| Trial Identity/<br>Report Date                                  | NCT No.                                | Trial Design                                                                                                             | Regimen/<br>Schedule/<br>Route                                                                                                                                                                                                                                                    | Study Endpoints                                         | Treatment Duration/<br>Follow Up                                                | No. of Patients Enrolled   | Study Population                                                                                                          | No. of Centers and Countries     |
|-----------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------|---------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| <b><i>Controlled studies to support efficacy and safety</i></b> |                                        |                                                                                                                          |                                                                                                                                                                                                                                                                                   |                                                         |                                                                                 |                            |                                                                                                                           |                                  |
| ESTEVE-SUSA-301 (83245) / 2018                                  | NCT03108482                            | Randomized, Double-blind, Active- and Placebo-controlled, Parallel Groups, Phase 3 study                                 | <ul style="list-style-type: none"> <li>• E-58425 200 mg every 12h</li> <li>• Tramadol 50 mg every 6h</li> <li>• Celecoxib 100 mg every 12h</li> <li>• Placebo every 6h</li> </ul> <p>Multiple dose / oral</p>                                                                     | Sum of pain intensity difference (SPID) from 0-48 hours | A maximum of 2 days / The last follow-up visit was done 5-9 days after surgery. | 637 (90 male, 547 female)  | Patients with moderate to severe post-operative pain after bunion-ectomy                                                  | Six centers in the United States |
| ESTEVE-SACO4-201 (82100) / 2013                                 | N/A (the study was conducted in Spain) | Randomized, Double-blind, Controlled with Active Treatment (Tramadol 100 mg) and Placebo, Parallel Groups, Phase 2 study | <ul style="list-style-type: none"> <li>• E-58425 50 mg</li> <li>• E-58425 100 mg</li> <li>• E-58425 150 mg</li> <li>• E-58425 200 mg</li> <li>• Adolonta (Tramadol HCl) 100-mg dose (2 x 50 mg oral capsule)</li> <li>• 2 tablets of placebo</li> </ul> <p>Single dose / Oral</p> | Sum of pain intensity difference (SPID) from 0-8 hours  | Single dose / The last follow-up visit was done 7 days after the procedure.     | 334 (142 male, 192 female) | Patients with moderate to severe dental pain after extraction of two or more impacted third molars requiring bone removal | Nine centers in Spain            |

Clinical Review  
NDA 213426  
E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

| <b>Trial Identity/<br/>Report Date</b>                                                                             | <b>NCT No.</b> | <b>Trial Design</b>                                                   | <b>Regimen/<br/>Schedule/<br/>Route</b>                                                         | <b>Study Endpoints</b> | <b>Treatment Duration/<br/>Follow Up</b>         | <b>No. of Patients Enrolled</b> | <b>Study Population</b>                 | <b>No. of Centers and Countries</b> |
|--------------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------|--------------------------------------------------|---------------------------------|-----------------------------------------|-------------------------------------|
| <b><i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i></b> |                |                                                                       |                                                                                                 |                        |                                                  |                                 |                                         |                                     |
| ESTEVE-SUSA-101 (ETV-P5-669) / 2017                                                                                | N/A            | Phase 1, single oral dose, bioavailability, fasting, cross-over study | • E-58425 200 mg (2 x 100-mg tablets)<br><br>Single dose / Oral                                 | N/A                    | Single dose / 48-hour follow up                  | 36                              | Healthy males and females (18-55 years) | One center in the United States     |
| ESTEVE-SACO4-103 (80845 or TAI-P0-692) / 2011                                                                      | N/A            | Phase 1, single oral dose, bioavailability, fasting, cross-over study | • E-58425 200 mg (2 x 100-mg tablets); Formulation 1 and 2<br><br>Single dose / Oral            | N/A                    | Single dose / 48-hour follow up                  | 12                              | Healthy males and females (18-55 years) | One center in Canada                |
| ESTEVE-SACO4-102 (80841 or TAI-P0-584) / 2011                                                                      | N/A            | Phase 1, single oral dose, bioavailability, fasting, cross-over study | • E-58425 200 mg (2 x 100-mg tablets)<br><br>Single dose / Oral                                 | N/A                    | Single dose / 48-hour follow up                  | 36                              | Healthy males and females (18-55 years) | One center in Canada                |
| ESTEVE-SACO4-104 (80877 or TAI-P1-585) / 2012                                                                      | N/A            | Phase 1, bioavailability fed/fasting, cross-over study                | • E-58425 200 mg (2 x 100-mg tablets) after fasting and fed condition<br><br>Single dose / Oral | N/A                    | Single dose / 48-hour follow up (blood sampling) | 36                              | Healthy males and females (18-55 years) | One center in Canada                |

Clinical Review

NDA 213426

E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

| <b>Trial Identity/<br/>Report Date</b>        | <b>NCT No.</b> | <b>Trial Design</b>                                                       | <b>Regimen/<br/>Schedule/<br/>Route</b>                                    | <b>Study Endpoints</b> | <b>Treatment Duration/<br/>Follow Up</b> | <b>No. of Patients Enrolled</b> | <b>Study Population</b>                 | <b>No. of Centers and Countries</b> |
|-----------------------------------------------|----------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------|------------------------------------------|---------------------------------|-----------------------------------------|-------------------------------------|
| ESTEVE-SACO4-105 (82608 or TAI-P3-526) / 2014 | N/A            | Phase 1, single and multiple oral dose, bioavailability, cross-over study | E-58425 200 mg (2 x 100 mg tablets) every 12 h<br><br>Multiple dose / Oral | N/A                    | Multiple dose (15 doses) / 7.5 days      | 32                              | Healthy males and females (18-50 years) | One center in Canada                |

Abbreviations: SPID – sum of pain intensity difference, NCT – National Clinical Trial

Source: reviewer-generated based on the Applicant's submission, 5.2. Tabular Listing of all Clinical Studies

**Table 2: Listing of Clinical Trials Performed by Mundipharma Research Ltd\***

| <b>Trial Identity</b> | <b>Title and Short Description</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | <b>Country</b>    |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| MR308-1501            | A Phase 1, open-label, three-period, randomized, crossover study to assess the pharmacokinetics and dose proportionality of single doses of Co-crystal E-58425 at 100 mg, 150 mg and 200 mg in Japanese and Caucasian healthy subjects (N=60)                                                                                                                                                                                                                                                                                | United Kingdom    |
| MR308-3501            | A Phase 3, randomized, double-blind, multicenter, placebo- and active comparator-controlled study to evaluate efficacy and safety of MR308 in the treatment of acute pain after third molar tooth extraction (STARDOM1)<br>A total of 726 patients were randomized into five treatment groups of CTC 100 mg BID, CTC 150 mg BID, CTC 200 mg BID, tramadol 100 mg BID, or placebo, according to a 2:2:2:2:1 randomization ratio. Primary efficacy endpoint was SPID 0-4 hours. Duration of double-blind treatment was 3 days. | Europe and Canada |
| MR308-3502            | A Phase 3, randomized, double-blind, multicenter, placebo- and active comparator-controlled study to evaluate efficacy and safety of MR308 in the treatment of acute pain after abdominal hysterectomy surgery under general anesthesia (STARDOM2)<br>A total of 1138 patients were randomized into six treatment groups of CTC 100 mg BID, CTC 150 mg BID, CTC 200 mg BID, tramadol 100 mg GID, celecoxib 100 mg BID, or placebo.                                                                                           | Europe and Canada |

\* Mundipharma Research Ltd is an independent third-party company that conducted one Phase 1 study and two Phase 3 studies outside the United States with celecoxib and tramadol, tablets, under the code name MR308 or CTC. The ISE and ISS do not include data from these studies. Any SAEs from these studies are included in the safety review.

Abbreviations: BID – twice daily, GID – four times daily, CTC – co-crystal tramadol celecoxib, SPID – sum of pain intensity difference

Source: reviewer-generated based on the Applicant's submission, 5.2. Tabular Listing of all Clinical Studies

## 5.2. Review Strategy

The Applicant submitted NDA 213426 through the 505(b)(2) regulatory pathway, relying on the FDA's previous findings of safety of Celebrex and Ultram as monotherapies, as well as original studies performed by the Applicant to support the use of E-58425 for the proposed indication of "the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate." The clinical studies performed by the Applicant to support the development of E-58425 included five Phase 1 studies, one Phase 2 study, and one Phase 3 study, as shown in Table 1.

The Applicant stated that all studies were performed according to the requirements of current GCP standards and in accordance with the ethical principles of the Declaration of Helsinki. The Applicant also stated that the studies not conducted under the IND were consistent with applicable local regulatory requirements and laws, as addressed in the guidance for industry and FDA staff *FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions* (March 2012).

The efficacy review includes a combined review performed by the statistical team and the clinical team that is focused on the Phase 3 study (ESTEVE-SUSA-301). Additionally, the results of the Phase 2 study (ESTEVE-SACO4-201) are discussed in the integrated summary of effectiveness.

The safety review includes review of all seven clinical studies submitted to this NDA, including five Phase 1 studies, one Phase 2 study, and one Phase 3 study. Additionally, any SAEs reported by MRL during the development program for the product outside the U.S. are included in the safety review.

## 6. Review of Relevant Individual Trials Used To Support Efficacy

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### 6.1. ESTEVE-SUSA-301 (83245)

#### 6.1.1. Study Design

##### Overview and Objective

The primary objective of this study was to establish the analgesic efficacy of E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain for 48 hours after bunionectomy by using assessments of pain intensity (PI).

The secondary objectives of the study included the following:

- To assess the analgesic efficacy of E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain at various time points after bunionectomy by using assessments of PI
- To assess the analgesic efficacy of E-58425 by means of responder rates, use of rescue medication, time to onset of analgesia, time to perceptible and meaningful PAR, time to onset of PI decrease, peak PAR and time to peak PAR, and subjects' overall assessment of the study medication
- To assess the absolute analgesic efficacy of E-58425 compared with placebo for the treatment of moderate to severe post-operative pain for 48 hours at various time points after bunionectomy by using assessments of PI
- To assess the safety and tolerability of the E-58425

## Trial Design

### Basic Study Design

Study ESTEVE-SUSA-301 was a randomized, double-blind, active- (tramadol and celecoxib) and placebo-controlled, parallel group, Phase 3 study in patients with moderate to severe pain after bunionectomy. This study served as a full factorial study to fulfill the requirement of the combination rule for the study drug, celecoxib and tramadol, tablet, or E-58425.

Table 3 and Table 4 show the study treatment arms and dosing scheme. Figure 1 shows the study design scheme.

**Table 3: Treatment Arms for Study ESTEVE-SUSA-301**

|                |                    |            | Total Daily Dose (mg) |           |
|----------------|--------------------|------------|-----------------------|-----------|
| Treatment Arms |                    | Posology   | Tramadol              | Celecoxib |
| ARM-1          | Co-crystal E-58425 | 200 mg BID | 176                   | 224       |
| ARM-2          | Tramadol           | 50 mg QID  | 200                   | 0         |
| ARM-3          | Celecoxib          | 100 mg BID | 0                     | 200       |
| ARM-4          | Placebo            | 0 mg QID   | 0                     | 0         |

Abbreviations: BID – twice daily (every 12 hours); QID – 4 times daily (every 6 hours)

Source: Adapted from Applicant's submission, NDA 213426, 2.7.6. Synopses of Individual Studies

**Table 4: Dosing Scheme for Study ESTEVE-SUSA-301**

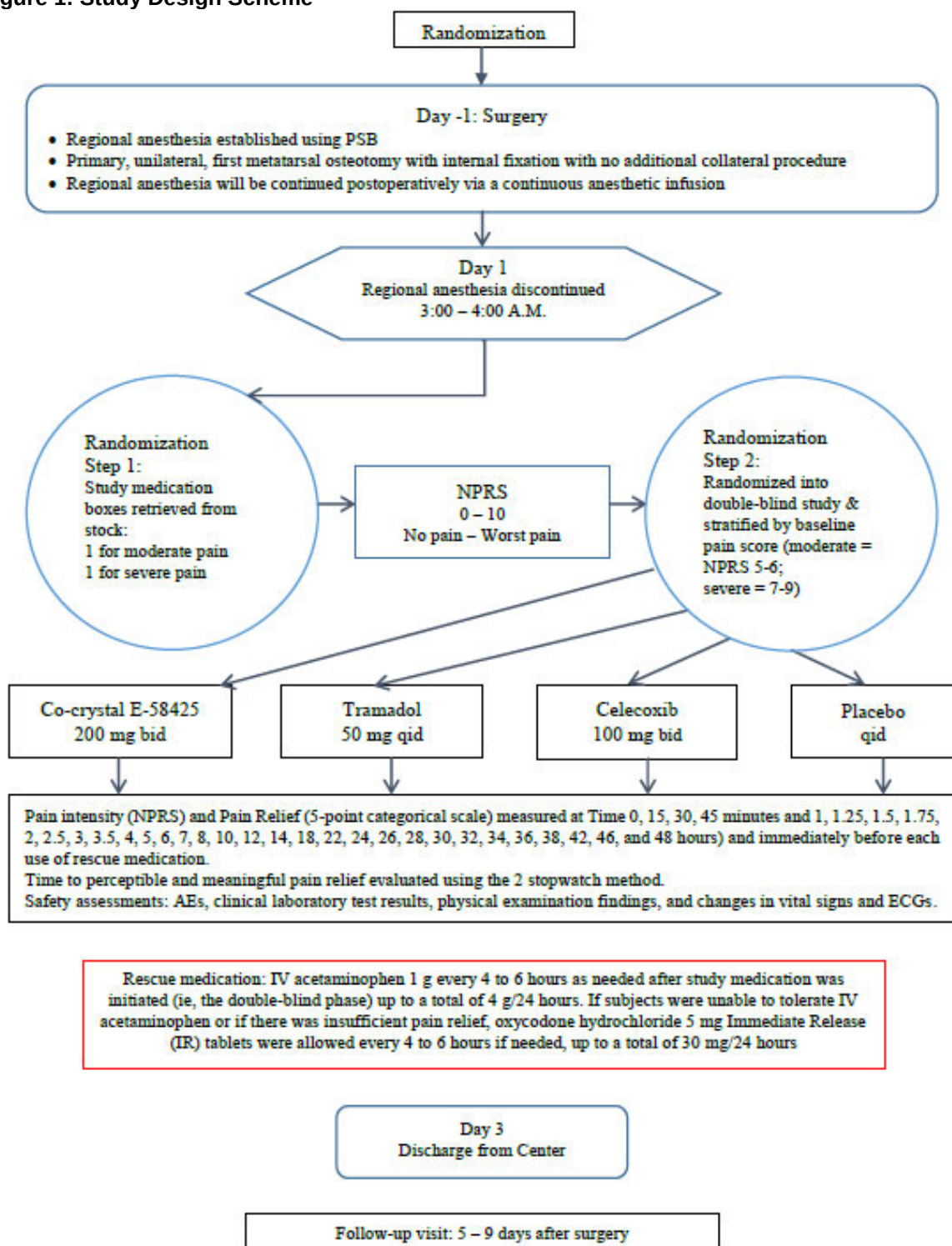
| Treatment Group    | Day 2 <sup>1</sup> |              |               |               | Day 3 <sup>1</sup> |               |               |               |
|--------------------|--------------------|--------------|---------------|---------------|--------------------|---------------|---------------|---------------|
|                    | Dose 1 (0 h)       | Dose 2 (6 h) | Dose 3 (12 h) | Dose 4 (18 h) | Dose 5 (24 h)      | Dose 6 (30 h) | Dose 7 (36 h) | Dose 8 (42 h) |
| Co-crystal E-58425 | 200                | P            | 200           | P             | 200                | P             | 200           | P             |
| Tramadol           | 50                 | 50           | 50            | 50            | 50                 | 50            | 50            | 50            |
| Celecoxib          | 100                | P            | 100           | P             | 100                | P             | 100           | P             |
| Placebo            | P                  | P            | P             | P             | P                  | P             | P             | P             |

<sup>1</sup> Doses measured in mg

Abbreviations: h – hour; P – placebo

Source: Adapted from Applicant's submission, NDA 213426, 2.7.6. Synopses of Individual Studies

Figure 1: Study Design Scheme



Abbreviations: PSB – popliteal sciatic nerve block, NPRS – Numerical Pain Rating Scale, BID – twice daily, QID – four times daily, AE – adverse events, ECG – electrocardiogram, IR – immediate release  
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301

### Study Location and Date

The study was conducted at six centers in the United States. The first subject was screened on (b) (6) and the last subject completed the study on (b) (6)

### Eligibility Criteria

Male and female subjects at least 18 years old, scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure, were eligible. Subjects who had a pain score of  $\geq 5$  and  $\leq 9$  on the 0-10 Numerical Pain Rating Scale (NPRS) at rest, after turning off the popliteal sciatic block, were eligible for randomization. Subjects who received any analgesic medication other than short-acting pre-operative or intra-operative anesthetic agents before the end of bunionectomy were excluded.

### Dose Selection, Study Arms, and Randomization

To fulfill the requirement of a full factorial study, Study ESTEVE-SUSA-301 included the following arms: active control tramadol arm, active control celecoxib arm, E-58425 arm, and placebo arm. After the surgery, eligible subjects were stratified by baseline pain score (moderate pain: NPRS 5-6; severe pain: NPRS 7-9) and were randomized to a study treatment arm in a 2:2:2:1 ratio.

- The subjects in the E-58425 arm took two tablets of E-58425 every 12 hours, i.e., celecoxib 112 mg and tramadol 88 mg, twice per day. The Applicant's rationale for dose selection of E-58425 was based on Study ESTEVE-SACO4-201 that is described in Section 6.2 of this review.
- The subjects in the celecoxib arm took Celebrex 100 mg every 12 hours, which is lower than the recommended dose of Celebrex for acute pain per its label. The recommended dosage of Celebrex for acute pain per its label is:
  - For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.
- The subjects in the tramadol arm took Ultram 50 mg every 6 hours, which is an acceptable regimen for use of tramadol in the clinical context of acute pain. The label for Ultram states the following:
  - For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

**Reviewer Comment:**

*The amount of celecoxib in each tablet of E-58425 is 56 mg. The E-58425 arm took 112 mg of celecoxib twice per day, with the total amount of celecoxib being 224 mg per day. The initial dose and maximum dose of celecoxib for both the Celebrex arm and the E-58425 arm are lower than the recommended dosage range for Celebrex label. Thus, the dosage of celecoxib for both the Celebrex arm and the E-58425 arm is subtherapeutic in the clinical context of acute pain.*

*The amount of tramadol in each tablet of E-58425 is 44 mg. The subjects in the E-58425 arm took 88 mg of tramadol twice per day, with the total amount of tramadol being 176 mg per day. The Ultram label notes that there is an increased risk of discontinuation due to AEs with higher initial doses, which includes the dose of tramadol in the E-58425 arm.*

Duration of Treatment/Follow-Up

Study medications were administered four times a day for a maximum of 2 days. Subjects were discharged from the study center at the end of the double-blind treatment period. Subjects returned for a follow-up visit 5 to 9 days after surgery.

Rescue Medication

Allowed rescue medications were acetaminophen 1 g intravenous every 4 to 6 hours, up to 4 g/24 hours, or oxycodone hydrochloride 5 mg IR tablet every 4 to 6 hours if needed, up to a total of 30 mg/24 hours.

**Study Endpoints**

The primary efficacy endpoint was the time-weighted SPID from 0 to 48 hours (SPID<sub>48</sub>). Pain intensity was measured by the NPRS with 0 indicating “No Pain” and 10 indicating “Worst Possible Pain.” In the study, each subject assessed his or her PI at Time 0, 15, 30, 45 minutes and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 42, 46, and 48 hours after Time 0, and immediately before each use of rescue analgesia. Pain assessment was performed during the night only if the subject was awake. In the study protocol it was stated that pain measurements were excluded from the analysis if they differed from the nominal time as follows:

- by >3 minutes in the first 2 hours,
- by >6 minutes after 2 hours and up to 4 hours,
- by >10 minutes after 4 hours and up to 8 hours, and
- by >15 minutes after 8 hours.

**Reviewer Comment:**

*The primary endpoint of SPID 48 was an appropriate primary efficacy endpoint that the Applicant used per the Division recommendation to provide evidence of efficacy over the first 48 hours of treatment.*

*In acute pain studies with subjects in hospital settings, there is usually a small percentage of subjects with missing pain scores. In the reviewed study, a pain assessment was not performed if the subject was sleeping during the night and pain measurements out of the assessment windows were excluded from the analysis, which resulted in a larger proportion of missing pain measurements than is typical for a study of this type.*

There were multiple secondary efficacy endpoints including the following:

- SPID (0-4 hours), SPID (0-6 hours), SPID (0-12 hours), and SPID (0-24 hours)
- PI difference (PID) at each time point (PIDt).  $PID_t = PI_t - PI_0$ , where  $PI_0$  is the PI at  $t=0$  hours and  $PI_t$  is the PI at specific time points. Positive values therefore correspond to an increase in pain, while negative values correspond to a decrease in pain.
- PI at each time point
- $PAR_t$  = PAR at each time point measured as 5-point categorical scale
- Peak PAR and time to peak PAR
- Time to onset of analgesia, time to perceptible PAR, and time to meaningful PAR (using stop watches)
- Time to onset of PI decrease
- Subjects' overall assessment of study medication
- Rescue medication use:
  - Proportion of subjects who took at least 1 dose of rescue medication up to 4, up to 6, up to 12, up to 24, and up to 48 hours after first dose of study medication; number of doses of rescue medication for the same time intervals
  - Time to first use of rescue medication
- Proportion of Responders, where Responders reached:
  - a 50% reduction in PI from baseline sustained until the end of the 48-hour observation period;
  - a 30% reduction in PI from baseline sustained until the end of the 48-hour observation period;
  - a PI below 4 on the NPRS sustained until the end of the 48-hour observation period;
  - a 50% reduction in PI compared with baseline and a PI below 4 on the NPRS sustained until the end of the 48-hour observation period;
  - a 30% reduction in PI compared with baseline and a PI below 4 on the NPRS sustained until the end of the 48-hour observation period.
- Time to first response was also analyzed as time-to-event data, using the first time at which each response criterion was reached by each subject

The safety endpoints included the following:

- Treatment-emergent AEs (TEAEs)
- Physical examination findings, clinical laboratory test results, and changes in vital sign and electrocardiograms (ECGs)

The proportion of subjects reporting at least one AE was compared between the treatment groups. Premature discontinuations for any reason and due to AEs were summarized by treatment group. Adverse events resulting in discontinuation of study medication and AEs of special interest were summarized separately in a similar manner. Laboratory, vital signs, and ECG data were described by summary tables and shift tables for out-of-range and clinically relevant values, as appropriate.

### Statistical Analysis Plan

The full analysis (FA) set included all subjects who underwent the complete randomization process and were assigned to a specific randomization stratum and to a unique treatment arm, irrespective of whether they actually received any dose of study medication. In the primary efficacy analysis, SPID<sub>48</sub> was compared between the treatment groups. Three separate null hypotheses were tested:

- The mean SPID<sub>48</sub> in the E-58425 group was equal to the mean SPID<sub>48</sub> in the tramadol group;
- The mean SPID<sub>48</sub> in the E-58425 group was equal to the mean SPID<sub>48</sub> in the celecoxib group;
- The mean SPID<sub>48</sub> in the E-58425 group was equal to the mean SPID<sub>48</sub> in the placebo group.

For a full factorial study to be declared successful, all three of those null hypotheses must have been rejected. Therefore, adjustment for multiple comparisons was not necessary. The hypotheses were tested in an analysis of covariance (ANCOVA) model including terms for treatment, center, and baseline pain (as a continuous variable). Estimates of least square (LS) means of the SPID<sub>48</sub> for each treatment group and estimates of the difference in LS means between the E-58425 group and each of the three control groups were calculated from the ANCOVA model, along with 95% CIs and p-values associated with those differences.

The intermittent missing PI scores were imputed by a linear interpolation method. For subjects who discontinued the study before 48 hours, the baseline observation carried forward (BOCF) method was used to impute missing PI scores after their withdrawal. The Applicant also conducted the following sensitivity analyses to impute missing PI scores in the study: the worst observation carried forward (WOCF) method for all dropouts; the WOCF method for dropouts due to related AEs or lack of efficacy, and the last observation carried forward (LOCF) method

for dropouts due to all other reasons; and a multiple imputation (MI) method. The Applicant called their MI method a jump to control MI analysis method, which is described as follows:

- i. For subjects in the placebo group, missing PI scores were imputed using the observed PI scores from placebo subjects at the same sites with similar baseline and post-baseline pain scores. The variables included in the imputation model were sex, center, baseline pain, and post-baseline pain. A minimum of 1,000 imputations were conducted.
- ii. For subjects in each active treatment group, the intermittent missing PI scores were firstly imputed assuming the intermittent missing values were missing at random. Then, the monotone post-withdrawal missing PI scores were imputed using a method proposed by O’Kelly (Ratitch and O’Kelly 2011). Missing PI scores at each timepoint were imputed using available PI scores for treated subjects and complete data for all placebo subjects (observed and imputed in step *i*) at that timepoint. A minimum of 1,000 imputations were conducted.
- iii. For each dataset containing imputed PI scores from step *i* and *ii*, E-58425 was compared with other treatment groups by an ANCOVA model using the terms treatment, center, and baseline pain. The ANCOVA results from the multiple imputed datasets were then combined using the Rubin’s rule (Little and Rubin 1987). A significance test of the treatment difference was performed at the two-sided 0.05 level and corresponding 95% CIs were calculated.

To account for the use of rescue medications, PI scores assessed immediately prior to rescue use were utilized to impute all scores observed in the 4 hours after the use of rescue medications. If subjects took analgesic medications during the study other than allowed rescue medications, all subsequent pain assessment were treated as missing and handled accordingly. A sensitivity analysis was also conducted in which all observed PI scores after the rescue use were analyzed as recorded.

**Reviewer comment:**

*As recommended in ICH E9 (R1) addendum, a primary estimand of interest should be prespecified for a clinical trial. The applicant did not specify the estimand of interest. However, in their MI method they stated, “The causal estimand will be estimated using the difference in the LS means between the co-crystal E-58425 group and the other treatment groups.”*

*The applicant used single imputation methods to impute missing PI scores in the study: the BOCF method in the primary efficacy analysis and the WOCF or LOCF method in the sensitivity analyses. However, as single imputation methods underestimate variability of imputations, they are not recommended by the National Academy of Science report on missing data. The MI method considered in the sensitivity analyses accounted for the variability of imputations. Moreover, it assigned bad outcomes to subjects discontinued the study due to AEs.*

## Protocol Amendments

There were three protocol amendments to the original protocol submission that included minor modifications. There were no significant changes to the safety measurements. The statistical analysis plan was revised twice. Summarized below are the protocol amendments related to the efficacy analyses:

### 1. Amendment 1.1 (dated August 26, 2016)

- The FA Set definition was changed from “all randomized subjects who provide at least 1 valid efficacy assessment (one PI assessment after the first dose of study medication)” to “all randomized subjects.”
- The visual analog scale (VAS) recorded on electronic patient diaries was replaced with an 11-point NPRS recorded on paper to assess PI during the study, and the qualifying NPRS were indicated.
- Added total PAR (TOTPAR) from 15 minutes – 4 hours to the secondary efficacy endpoints.
- Added rescue medication up to 4 hours to the secondary efficacy endpoints.
- Added time to onset of PI decrease to the secondary efficacy endpoints.
- Added Completers Analysis Set.
- Added extra time points for NPRS assessment.
- Added new secondary endpoint of time to onset of PI decrease.

### 2. Amendment 2.0 (dated November 09, 2016)

- Clarified the objective to reflect that analgesic efficacy was to be established over a period of 48 hours, not the first 48 hours after the bunionectomy.

## 6.1.2. Study Results

### Compliance With Good Clinical Practices

The Applicant stated that all studies were performed according to the requirements of current GCP standards and in accordance with the ethical principles of the Declaration of Helsinki.

### Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

### Patient Disposition

A total of 693 subjects were enrolled, defined as subjects who completed randomization step 1 (initial assignment). A total of 56 subjects were not assigned to a unique treatment arm,

primarily due to not meeting required pain scores. A total of 637 subjects were randomized to a unique treatment arm, including 90 (14.1%) male and 547 (85.9%) female subjects. Given the bunionectomy procedure as the pain model, the higher ratio of female subjects in this study is not unexpected. A total of 628 subjects completed the study, defined as completion of all visits/assessments regardless of study medication discontinuation. A total of 17 subjects discontinued study medication but completed all visits. A total of 9 subjects withdrew from the study, defined as not completing all visits/assessments, regardless of study medication discontinuation. Figure 2 shows disposition of study subjects in Study ESTEVE-SUSA-301. Three subjects completed treatment but did not attend the follow-up visit. The FA set included 637 patients, for both efficacy and safety analysis. An overview of the number of subjects who discontinued study medication or withdrew from the study is given in Table 5.

**Table 5: Summary of Reasons for Discontinuation of Study Medications or Withdrawal From Study**

| <b>Study Medication Discontinuations or Withdrawals from the Study</b> | <b>E-58425 (N=183) n (%)</b> | <b>Tramadol (N=183) n (%)</b> | <b>Celecoxib (N=182) n (%)</b> | <b>Placebo (N=89) n (%)</b> | <b>Total (N=637) n (%)</b> |
|------------------------------------------------------------------------|------------------------------|-------------------------------|--------------------------------|-----------------------------|----------------------------|
| Discontinuation of study medication                                    | 7 (3.8)                      | 1 (0.5)                       | 6 (3.3)                        | 3 (3.4)                     | 17 (2.7)                   |
| Reason <sup>a</sup> :                                                  |                              |                               |                                |                             |                            |
| Withdrawal by subject                                                  | 2 (1.1) <sup>b</sup>         | 1 (0.5) <sup>c</sup>          | 2 (1.1)                        | 0                           | 5 (0.8)                    |
| Adverse event                                                          | 1 (0.5) <sup>d</sup>         | 0                             | 0                              | 0                           | 1 (0.2)                    |
| Unspecified reasons                                                    | 4 (2.2) <sup>e</sup>         | 0                             | 4 (2.2)                        | 3 (3.4)                     | 11 (1.7)                   |
| Withdrawals from study                                                 | 0                            | 4 (2.2)                       | 2 (1.1)                        | 3 (3.4)                     | 9 (1.4)                    |
| Reason:                                                                |                              |                               |                                |                             |                            |
| Adverse event                                                          | 0                            | 1 (0.5) <sup>f</sup>          | 0                              | 0                           | 1 (0.2)                    |
| Lack of efficacy                                                       | 0                            | 0                             | 0                              | 1 (1.1)                     | 1 (0.2)                    |
| Lost to follow-up <sup>g</sup>                                         | 0                            | 1 (0.5)                       | 2 (1.1)                        | 0                           | 3 (0.5)                    |
| Protocol deviation                                                     | 0                            | 1 (0.5)                       | 0                              | 0                           | 1 (0.2)                    |
| Withdrawal by subject                                                  | 0                            | 1 (0.5) <sup>h</sup>          | 0                              | 2 (2.2)                     | 3 (0.5)                    |
| <b>Total</b>                                                           | <b>7 (3.8)</b>               | <b>5 (2.7)</b>                | <b>8 (4.4)</b>                 | <b>6 (6.7)</b>              | <b>26 (4.1)</b>            |

<sup>a</sup> Reasons for discontinuation of study medication were entered by the investigator as free text, and were grouped for this table.

<sup>b</sup> Subject (b) (6) had an AE that led to discontinuation of study medication.

<sup>c</sup> Subject (b) (6) had an AE that led to discontinuation of study medication.

<sup>d</sup> Subject (b) (6) had an AE that led to discontinuation of study medication.

<sup>e</sup> Subject (b) (6) had an AE that led to discontinuation of study medication.

<sup>f</sup> Subject (b) (6) had an AE that led to discontinuation of study medication.

<sup>g</sup> Received all 8 doses of study medication and included in PPAS.

<sup>h</sup> Subject (b) (6) had an AE that led to discontinuation of study medication.

Abbreviations: PPAS – per-protocol analysis set

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 10-1.

**Figure 2: Disposition of Subjects for Study ESTEVE-SUSA-301**

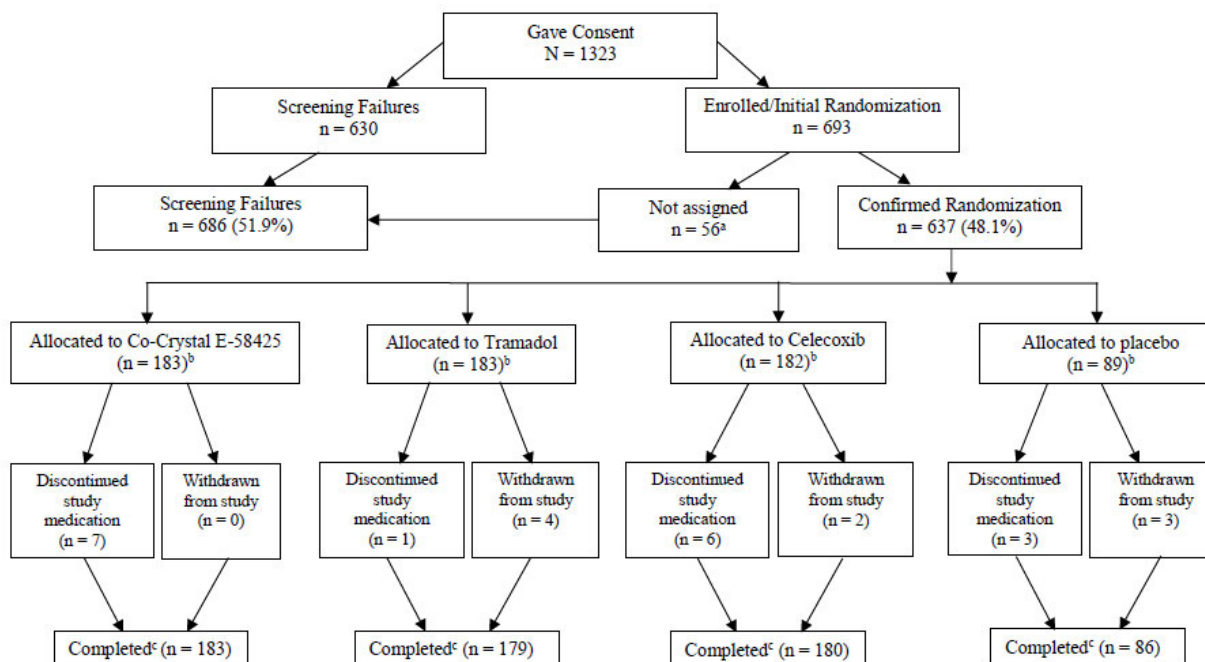


**Figure 10-1: Disposition of Subjects (All Subjects)**

Source: Section 14.1, Table 14.1.3, Table 14.1.5; Table 14.1.7; Appendix 16.2, Listing 16.2.1.2; Listing 16.2.1.3

a Not assigned to a unique treatment arm/strata primarily due to not meeting required pain scores (<5 or >9 on a 0-10 NPRS) per Inclusion Criterion #6/Exclusion Criterion #1.

b Safety Analysis Set, based on the treatment received. Three subjects were misrandomized; they are evaluated in the FAS based on the treatment to which they were assigned: 184 subjects in co-crystal E-58425, 183 subjects in tramadol, 181 subjects in celecoxib, and 89 subjects in the placebo group.

c Per Table 14.1.3

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301

## Protocol Violations/Deviations

Three subjects were mis-randomized, but they were evaluated in the efficacy analyses based on the treatment they received. The proportion of subjects with major protocol deviations or excluded from the per-protocol (PP) analysis set is listed in Table 6. The placebo group had the highest proportion of subjects with major protocol deviations (9%).

**Table 6: Subjects With Major Protocol Deviation or Excluded From the Per-Protocol Analysis Set**

|                                                                 | <b>E-58425<br/>(N=183)<br/>n (%)</b> | <b>Tramadol<br/>(N=183)<br/>n (%)</b> | <b>Celecoxib<br/>(N=182)<br/>n (%)</b> | <b>Placebo<br/>(N=89)<br/>n (%)</b> | <b>Total<br/>(N=637)<br/>n (%)</b> |
|-----------------------------------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|------------------------------------|
| <b>Major Protocol Deviations</b>                                |                                      |                                       |                                        |                                     |                                    |
| Subjects with a major protocol deviation detected by monitoring | 11 (6.0)                             | 3 (1.6)                               | 9 (5.0)                                | 8 (9.0)                             | 31 (4.9) <sup>a</sup>              |
| Subjects enrolled without satisfying entry criteria             | 1 (0.5) <sup>b</sup>                 | 0                                     | 0                                      | 0                                   | 0                                  |
| Subjects who received the wrong treatment or incorrect dose     | 1 (0.5) <sup>c</sup>                 | 0                                     | 1 (0.5) <sup>d</sup>                   | 0                                   | 2 (0.3)                            |
| Subjects excluded from the PP analysis                          | 32 (17.4)                            | 37 (20.2)                             | 39 (21.5)                              | 23 (25.8)                           | 131 (20.6)                         |

<sup>a</sup> Not all of these subjects were excluded from the PPAS.

<sup>b</sup> Subject (b) (6) had a BMI of 40.1 (Inclusion Criterion #5); this subject is included in the FAS, but is excluded from the PPAS due to discontinuation of study medication.

<sup>c</sup> Subject (b) (6): Correctly randomized to co-crystal E-58425, but her third dose was accidentally taken from another subject's kit (Subject (b) (6), which was actually tramadol

<sup>d</sup> Subject (b) (6): The subject should have been given co-crystal E-58425, but was actually given celecoxib.

Abbreviation: PP – per protocol

Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 10-3.

## Table of Demographic Characteristics

The treatment groups in the FA set were similar at baseline with regard to mean age, body weight, height, body mass index (BMI), sex, and ethnicity. Table 7 shows the demographic data for subjects in the safety analysis set of Study ESTEVE-SUSA-301. Overall, the mean age was approximately 46 years. The majority of subjects in the study were female (85.9%), white (73.8%), and not Hispanic or Latino (76.3%). The four treatment groups were similar with regard to baseline characteristics. shows the demographic data for study ESTEVE-SUSA-301. Overall, the mean age was approximately 46 years (range: 43.9 to 48.1). Nine percent (9%) of all study subjects (58 subjects) were over 65 years of age and the co-crystal group had the lowest proportion of subjects over 65 years of age (6%, 11 subjects) among different treatment arms.

### Reviewer Comment:

*Only a small number of subjects (58 subjects, 9%) were over 65 years of age in this study and only 6% of subjects in co-crystal group were over 65 years of age.*

**Table 7: Demographic Data (Safety Analysis Set)**

| <b>Variable/Sample Characteristic</b>     | <b>Co-crystal E-58425 (N=183)</b> | <b>Tramadol (N=183)</b> | <b>Celecoxib (N=182)</b> | <b>Placebo (N=89)</b> | <b>Total (N=637)</b> |
|-------------------------------------------|-----------------------------------|-------------------------|--------------------------|-----------------------|----------------------|
| Age [years]                               |                                   |                         |                          |                       |                      |
| n                                         | 183                               | 183                     | 182                      | 89                    | 637                  |
| Mean                                      | 43.9                              | 48.1                    | 45.1                     | 46.1                  | 45.8                 |
| SD                                        | 14.48                             | 14.36                   | 12.97                    | 14.90                 | 14.15                |
| Minimum                                   | 18                                | 18                      | 18                       | 21                    | 18                   |
| Median                                    | 45.0                              | 51.0                    | 46.0                     | 50.0                  | 47.0                 |
| Maximum                                   | 77                                | 77                      | 77                       | 75                    | 77                   |
| Age group, n (%)                          |                                   |                         |                          |                       |                      |
| <65 years                                 | 172 (94.0)                        | 159 (86.9)              | 166 (91.2)               | 82 (92.1)             | 579 (90.0)           |
| >65 years                                 | 11 (6.0)                          | 24 (13.1)               | 16 (8.8)                 | 7 (7.9)               | 58 (9.1)             |
| Body weight [kg]                          |                                   |                         |                          |                       |                      |
| n                                         | 183                               | 183                     | 182                      | 89                    | 637                  |
| Mean                                      | 76.82                             | 74.97                   | 76.33                    | 76.32                 | 76.08                |
| SD                                        | 16.091                            | 15.738                  | 16.838                   | 15.766                | 16.143               |
| Minimum                                   | 45.8                              | 49.2                    | 47.0                     | 46.7                  | 45.8                 |
| Median                                    | 75.75                             | 72.12                   | 73.45                    | 74.39                 | 73.48                |
| Maximum                                   | 148.8                             | 128.8                   | 139.7                    | 117.6                 | 148.8                |
| Height [cm]                               |                                   |                         |                          |                       |                      |
| n                                         | 183                               | 183                     | 182                      | 89                    | 637                  |
| Mean                                      | 165.12                            | 164.60                  | 165.08                   | 165.58                | 165.02               |
| SD                                        | 8.376                             | 8.108                   | 9.183                    | 9.090                 | 8.627                |
| Minimum                                   | 142.2                             | 146.8                   | 146.0                    | 147.3                 | 142.2                |
| Median                                    | 163.82                            | 163.83                  | 164.60                   | 165.10                | 165.00               |
| Maximum                                   | 196.9                             | 185.4                   | 200.7                    | 197.0                 | 200.7                |
| BMI [kg/m <sup>2</sup> ]                  |                                   |                         |                          |                       |                      |
| n                                         | 183                               | 183                     | 182                      | 89                    | 637                  |
| Mean                                      | 28.09                             | 27.59                   | 27.92                    | 27.82                 | 27.86                |
| SD                                        | 4.989                             | 4.881                   | 5.100                    | 5.172                 | 5.008                |
| Minimum                                   | 18.9                              | 18.3                    | 17.1                     | 18.2                  | 17.1                 |
| Median                                    | 27.80                             | 27.40                   | 27.80                    | 27.10                 | 27.50                |
| Maximum                                   | 39.9                              | 39.5                    | 39.5                     | 40.1                  | 40.1                 |
| Sex, n (%)                                |                                   |                         |                          |                       |                      |
| Male                                      | 22 (12.0)                         | 33 (18.0)               | 21 (11.6)                | 14 (15.7)             | 90 (14.1)            |
| Female                                    | 161 (88.0)                        | 150 (82.0)              | 161 (88.5)               | 75 (84.3)             | 547 (85.9)           |
| Ethnicity, n (%)                          |                                   |                         |                          |                       |                      |
| Hispanic or Latino                        | 50 (27.2)                         | 45 (24.6)               | 38 (21.0)                | 18 (20.2)             | 151 (23.7)           |
| Not Hispanic or Latino                    | 133 (72.7)                        | 138 (75.4)              | 144 (79.1)               | 71 (79.8)             | 486 (76.3)           |
| Race, n (%)                               |                                   |                         |                          |                       |                      |
| American Indian or Alaska Native          | 1 (0.5)                           | 2 (1.1)                 | 2 (1.1)                  | 0                     | 5 (0.8)              |
| Asian                                     | 2 (1.1)                           | 14 (7.7)                | 8 (4.4)                  | 3 (3.4)               | 27 (4.2)             |
| Black or African American                 | 42 (23.0)                         | 40 (21.9)               | 33 (18.1)                | 20 (22.5)             | 135 (21.2)           |
| Native Hawaiian or Other Pacific Islander | 5 (2.7)                           | 1 (0.5)                 | 1 (0.5)                  | 1 (1.1)               | 8 (1.3)              |
| White                                     | 138 (74.9)                        | 128 (69.9)              | 139 (76.4)               | 66 (74.2)             | 470 (73.8)           |
| Other                                     | 1 (0.5)                           | 1 (0.5)                 | 2 (1.1)                  | 0                     | 4 (0.6)              |

Note: Categories of race were not mutually exclusive; categories may sum to more than 100%

Abbreviations: BMI – body mass index

Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline pain scores are displayed in Table 8 for all four treatment groups. There was no imbalance in the baseline pain scores across treatment groups.

**Table 8: Baseline Pain Group (Full Analysis Set)**

|                            | <b>Co-crystal<br/>E-58425<br/>(N=183)<br/>n (%)</b> | <b>Tramadol<br/>(N=183)<br/>n (%)</b> | <b>Celecoxib<br/>(N=182)<br/>n (%)</b> | <b>Placebo<br/>(N=89)<br/>n (%)</b> | <b>Total<br/>(N=637)<br/>n (%)</b> |
|----------------------------|-----------------------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|------------------------------------|
| <b>Baseline Pain Score</b> |                                                     |                                       |                                        |                                     |                                    |
| Moderate (NPRS 5-6)        | 89 (48.4)                                           | 90 (49.2)                             | 86 (47.5)                              | 42 (47.2)                           | 307 (48.2)                         |
| Severe (NPRS 7-9)          | 95 (51.6)                                           | 93 (50.8)                             | 95 (52.5)                              | 47 (52.8)                           | 330 (51.8)                         |

Abbreviation: NPRS – Numerical Pain Rating Scale

Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 10-6.

### Treatment Compliance and Concomitant Medications

Table 9 provides a summary of exposure and compliance to study products. The mean (SD) number of doses was 7.8 (1.06). Across the treatment groups, the median duration of exposure was 42 hours in each treatment group. The tramadol group had the longest mean duration of exposure at 41.37 hours, while the placebo group had the shortest mean duration of exposure (39.64 hours). Mean compliance with study medication was 97.61% for the overall subjects, with the placebo group having the least compliance (95.08%).

**Table 9: Summary of Exposure and Compliance to Study Products**

| <b>Sample<br/>Characteristic</b> | <b>E-58425<br/>(N=183)</b> | <b>Tramadol<br/>(N=183)</b> | <b>Celecoxib<br/>(N=182)</b> | <b>Placebo<br/>(N=89)</b> | <b>Total<br/>(N=637)</b> |
|----------------------------------|----------------------------|-----------------------------|------------------------------|---------------------------|--------------------------|
| Number of doses taken            |                            |                             |                              |                           |                          |
| n                                | 183                        | 183                         | 182                          | 89                        | 637                      |
| Mean                             | 7.8                        | 7.9                         | 7.8                          | 7.6                       | 7.8                      |
| SD                               | 0.92                       | 0.75                        | 1.17                         | 1.54                      | 1.06                     |
| Minimum                          | 1                          | 1                           | 1                            | 1                         | 1                        |
| Median                           | 8.0                        | 8.0                         | 8.0                          | 8.0                       | 8.0                      |
| Maximum                          | 8                          | 8                           | 9                            | 8                         | 8                        |
| Duration of exposure [hours]     |                            |                             |                              |                           |                          |
| n                                | 183                        | 183                         | 182                          | 89                        | 637                      |
| Mean                             | 41.05                      | 41.37                       | 40.71                        | 39.64                     | 40.85                    |
| SD                               | 5.490                      | 4.514                       | 7.032                        | 9.249                     | 6.377                    |
| Minimum                          | 0                          | 0                           | 0                            | 0                         | 0                        |
| Median                           | 42.00                      | 42.00                       | 42.00                        | 42.00                     | 42.00                    |
| Maximum                          | 42.5                       | 42.2                        | 42.1                         | 42.0                      | 42.5                     |

| <b>Sample Characteristic</b> | <b>E-58425 (N=183)</b> | <b>Tramadol (N=183)</b> | <b>Celecoxib (N=182)</b> | <b>Placebo (N=89)</b> | <b>Total (N=637)</b> |
|------------------------------|------------------------|-------------------------|--------------------------|-----------------------|----------------------|
| Compliance [%]               |                        |                         |                          |                       |                      |
| n                            | 183                    | 183                     | 182                      | 89                    | 637                  |
| Mean                         | 98.02                  | 98.70                   | 97.32                    | 95.08                 | 97.61                |
| SD                           | 11.439                 | 9.405                   | 14.651                   | 19.275                | 13.287               |
| Minimum                      | 12.5                   | 12.5                    | 12.5                     | 12.5                  | 12.5                 |
| Median                       | 100.00                 | 100.00                  | 100.00                   | 100.00                | 100.00               |
| Maximum                      | 100.0                  | 100.0                   | 100.0                    | 100.0                 | 100.0                |

Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 10-8.

Subjects were discharged from the study site with prescriptions for pain medication which were recorded as concomitant medication. Therefore, it is not unexpected that 94% of subjects used concomitant medications during the study, with similar rates across the treatment groups (91 to 96%). The most common concomitant medications were opioids (59.2%), and all treatment groups had similar proportions of subjects using opioids. The use of opioids as concomitant medication excludes oxycodone given as rescue medication in 56% of subjects at any time of their stay in the study center. Among those subjects who used concomitant opioids, Vicodin (hydrocodone bitartrate/paracetamol) was used by approximately 40% of subjects in each treatment group, and PROCET/01554201 (hydrocodone/paracetamol) was used by approximately 15 to 20% of subjects in each group. Non-steroidal anti-inflammatory and anti-rheumatic products were the next most used as concomitant medications, and were used by approximately 55% of subjects in each treatment group, with ibuprofen being the most common.

Over half the subjects in each treatment group used ibuprofen, an overall proportion of 53%. Paracetamol was used by 9 to 13% of subjects across the groups, and acetylsalicylic acid was used by 1 to 2% of subjects across the groups.

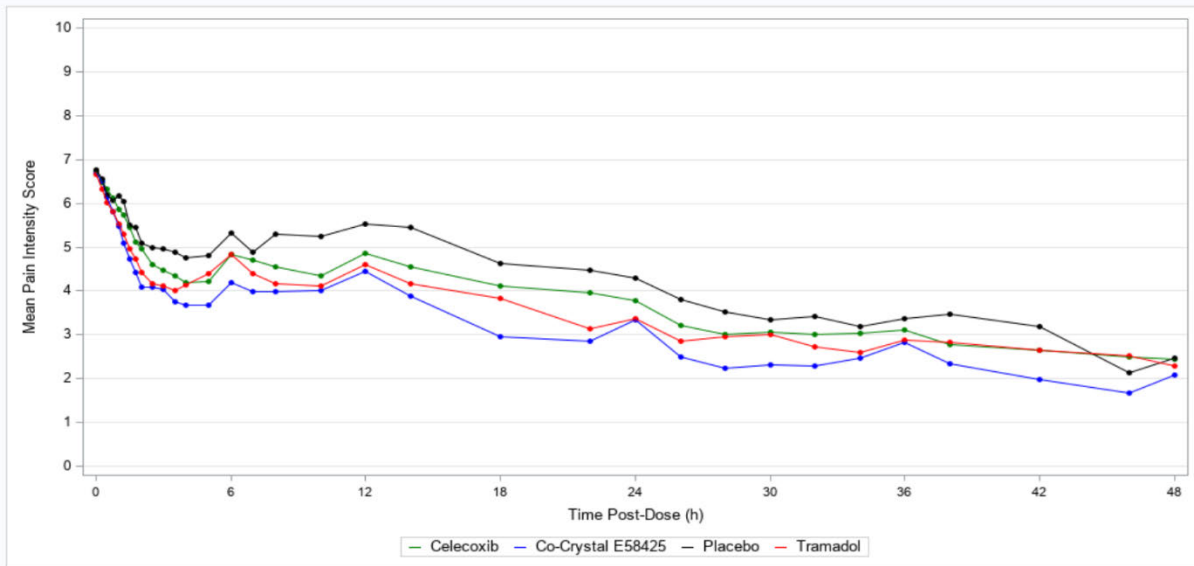
Antiemetics and antinauseants were used more in the E-58425 and tramadol groups (21% and 22%, respectively) than in the celecoxib and the placebo groups (7% and 6%, respectively). The most common antiemetic medication was ondansetron, used by 30 (16.4%) subjects in the E-58425 group, 36 (19.7%) subjects in the tramadol group, 10 (5.5%) subjects in the celecoxib group, and 4 (4.5%) subjects in the placebo group. In addition, ondansetron hydrochloride was used by 7 (3.8%) subjects in the E-58425 group, 3 (1.6%) subjects in the tramadol group, 3 (1.6%) subjects in the celecoxib group, and 1 (1.1%) subjects in the placebo group.

### **Efficacy Results – Primary Endpoint**

There were 184 subjects from the E-58425 treatment group, 183 subjects from the tramadol group, 181 subjects from the celecoxib group, and 89 subjects from the placebo group included in the FA set. The mean observed PI scores over the 48-hour post-operative period for each treatment group are displayed in Figure 3. At all timepoints through 48 hours, the means of observed PI scores were lower in the E-58425 group compared with all other treatment groups.

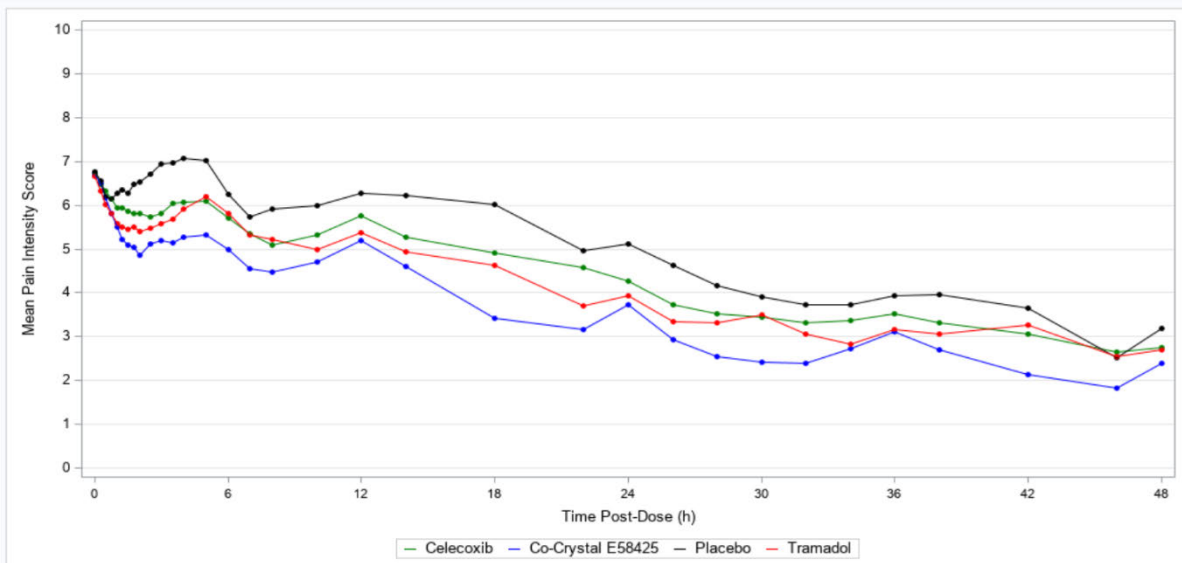
Figure 4 shows the mean of PI scores for each treatment group where the PI scores observed within 4 hours after the use of rescue medications were imputed by the PI scores recorded immediately prior to rescue use. In Figure 4, the means of PI scores were still lower in the E-58425 group compared with all other three treatment groups.

**Figure 3: Mean PI Scores Over Time (Using Observed PI Scores)**



Source: Reviewer's analysis results.

**Figure 4: Mean PI Scores Over Time (Pre-Rescue PI Score Was Imputed up to 4 Hours After Rescue Use)**



Source: Reviewer's analysis results.

The reviewer was able to reproduce the Applicant's analyses of the primary efficacy endpoint where missing PI scores were imputed by the BOCF method and the PI scores observed within 4 hours after the use of rescue medications were imputed by the PI scores recorded immediately prior to rescue use. Results from the ANCOVA model are shown in Table 10. The E-58425 group had statistically significantly better mean SPID<sub>48</sub> scores than any of the other groups after bunionectomy.

**Table 10: SPID<sub>48</sub>: Primary Analysis Results (BOCF Method)**

| Treatment | LS Mean | 95% CI of LS mean  | Comparison              | P-Value | Estimate of Difference in LS Means | 95% CI for Difference in LS Means |
|-----------|---------|--------------------|-------------------------|---------|------------------------------------|-----------------------------------|
| E-58425   | -139.12 | (-151.75, -126.49) |                         |         |                                    |                                   |
| Tramadol  | -109.08 | (-121.74, -96.42)  | E-58425 minus tramadol  | 0.0008  | -30.04                             | (-47.47, -12.61)                  |
| Celecoxib | -103.69 | (-116.39, -90.99)  | E-58425 minus celecoxib | <0.0001 | -35.45                             | (-52.90, -17.95)                  |
| Placebo   | -74.55  | (-92.48, -56.61)   | E-58425 minus placebo   | <0.0001 | -64.57                             | (-86.12, -43.02)                  |

Abbreviations: BOCF – baseline observation carried forward; LS – least square; SPID – sum of pain intensity difference  
Source: Reviewer's analysis results.

As was noted in the previous section discussing the primary endpoint, there were a lot of missing data in the study because pain measurements out of the assessment windows were excluded from the analysis and subjects were not woken during the night to collect pain assessments. For example, there were approximately 47% of subjects with the Hour 22 assessment missing and approximately 46% of subjects with the Hour 46 assessment missing. Given such a large proportion of missing data, the single imputation BOCF method in the primary analysis underestimated the variability of imputation. The MI method described in the previous section of the statistical analysis plan counted for the imputation variability. Moreover, it assigned bad outcomes to the subjects discontinued due to AEs. The reviewer's results from the MI method are shown in Table 11. These are slightly different from those of the Applicant, as the Applicant did not set the range (between 0 and 10) for the imputed PI scores. Furthermore, the Applicant only did linear interpolation for missing PI scores at Hour 22 and 46, while the reviewer did linear interpolation for missing PI scores at all time points. Nevertheless, the E-58425 group had statistically significantly better mean SPID<sub>48</sub> scores than any of the other groups after bunionectomy.

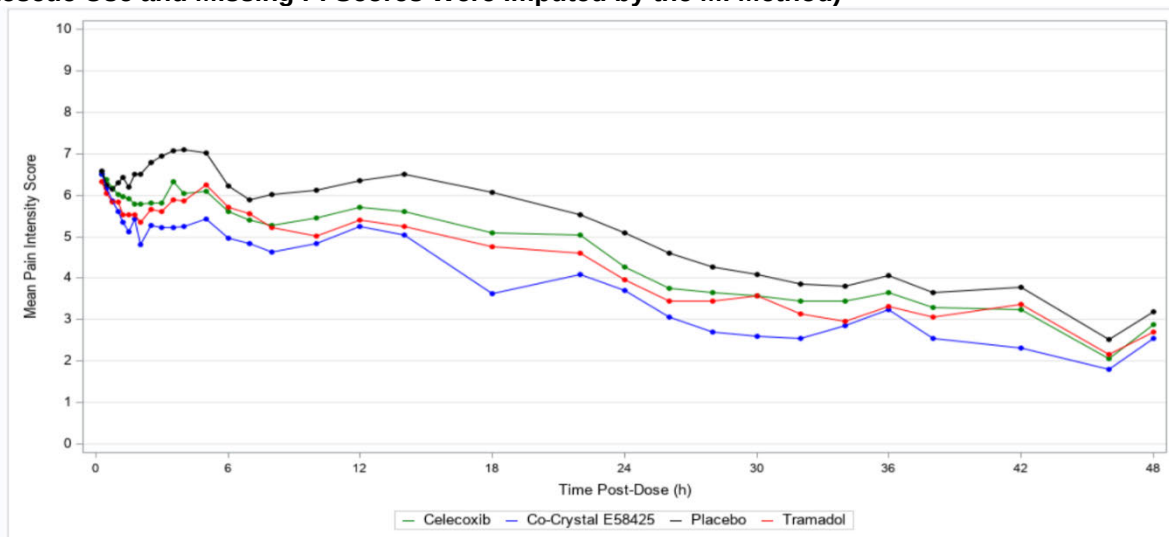
Figure 5 shows the mean of PI scores for each treatment group where the PI scores observed within 4 hours after the use of rescue medications were imputed by the PI scores recorded immediately prior to rescue use and missing PI scores were imputed by the MI method. In Figure 5, the means of PI scores were still lower in the E-58425 group compared with the other three treatment groups.

**Table 11: SPID<sub>48</sub>: Analysis Results From the MI Method**

| Treatment | LS Mean | 95% CI of LS Mean  | Comparison              | P-Value | Estimate of Difference in LS Means | 95% CI for Difference in LS Means |
|-----------|---------|--------------------|-------------------------|---------|------------------------------------|-----------------------------------|
| E-58425   | -130.63 | (-142.16, -119.11) |                         |         |                                    |                                   |
| Tramadol  | -105.53 | (-117.10, -93.96)  | E-58425 minus Tramadol  | 0.0015  | -25.10                             | (-40.59, -9.61)                   |
| Celecoxib | -97.42  | (-109.14, -85.71)  | E-58425 minus Celecoxib | <0.0001 | -33.20                             | (-48.78, -17.64)                  |
| Placebo   | -66.98  | (-84.14, -49.82)   | E-58425 minus placebo   | <0.0001 | -63.65                             | (-83.44, -43.86)                  |

Abbreviation: LS – least square  
Source: Reviewer's analysis results.

**Figure 5: Mean PI Scores Over Time (Pre-Rescue PI Score Was Imputed up to 4 Hours After Rescue Use and Missing PI Scores Were Imputed by the MI Method)**



Source: Reviewer's analysis results.

## Data Quality and Integrity

This study was started before (b) (6). The electronic datasets and define files submitted by the Applicant were of acceptable quality.

## Efficacy Results – Secondary and Other Relevant Endpoints

The reviewer analyzed three secondary efficacy endpoints: rescue medication use, time to the first rescue use, and time to meaningful PAR.

### Rescue Medication Use

As displayed in Table 12, a total of 83.5% of subjects used rescue medication at some point during the study. The majority of subjects used acetaminophen as rescue medication (82.7%), and approximately half the subjects used oxycodone hydrochloride (55.9%). When compared across treatment groups, the E-58425 group had the smallest proportion of subjects using rescue medications at any time point.

**Table 12: Rescue Medication Use (Full Analysis Set)**

| <b>Time/ Type of Rescue Medication</b> | <b>E-58425<br/>(N=184)<br/>n (%)</b> | <b>Tramadol<br/>(N=183)<br/>n (%)</b> | <b>Celecoxib<br/>(N=181)<br/>n (%)</b> | <b>Placebo<br/>(N=89)<br/>n (%)</b> | <b>Total<br/>(N=637)<br/>n (%)</b> |
|----------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|------------------------------------|
| Any Rescue medication at any time      | 140 (76.1)                           | 153 (83.6)                            | 160 (88.4)                             | 79 (88.8)                           | 532 (83.5)                         |
| Acetaminophen                          | 138 (75.0)                           | 151 (82.5)                            | 159 (87.8)                             | 79 (88.8)                           | 527 (82.7)                         |
| Oxycodone HCl                          | 77 (41.8)                            | 100 (54.6)                            | 117 (64.6)                             | 62 (69.7)                           | 356 (55.9)                         |
| Other                                  | 1 (0.5)                              | 0                                     | 0                                      | 0                                   | 1 (0.2)                            |
| Within first 4 hours after dosing      | 91 (49.5)                            | 113 (61.7)                            | 118 (65.2)                             | 67 (75.3)                           | 389 (61.1)                         |
| Acetaminophen                          | 91 (49.5)                            | 113 (61.7)                            | 117 (64.6)                             | 67 (75.3)                           | 388 (60.9)                         |
| Oxycodone HCl                          | 27 (14.7)                            | 49 (26.8)                             | 61 (33.7)                              | 31 (34.8)                           | 168 (26.4)                         |
| Within first 6 hours after dosing      | 102 (55.4)                           | 131 (71.6)                            | 126 (69.6)                             | 71 (79.8)                           | 430 (67.5)                         |
| Acetaminophen                          | 101 (54.9)                           | 131 (71.6)                            | 125 (69.1)                             | 71 (79.8)                           | 428 (67.2)                         |
| Oxycodone HCl                          | 37 (20.1)                            | 58 (31.7)                             | 67 (37.0)                              | 38 (42.7)                           | 200 (31.4)                         |
| Other                                  | 1 (0.5)                              | 0                                     | 0                                      | 0                                   | 1 (0.2)                            |
| Within first 12 hours after dosing     | 132 (71.7)                           | 148 (80.9)                            | 152 (84.0)                             | 76 (85.4)                           | 508 (79.7)                         |
| Acetaminophen                          | 130 (70.7)                           | 147 (80.3)                            | 152 (84.0)                             | 76 (85.4)                           | 505 (79.3)                         |
| Oxycodone HCl                          | 55 (29.9)                            | 71 (38.8)                             | 90 (49.7)                              | 50 (56.2)                           | 266 (41.8)                         |
| Other                                  | 1 (0.5)                              | 0                                     | 0                                      | 0                                   | 1 (0.2)                            |
| Within first 24 hours after dosing     | 139 (75.5)                           | 152 (83.1)                            | 158 (87.3)                             | 79 (88.8)                           | 528 (82.9)                         |
| Acetaminophen                          | 138 (75.0)                           | 151 (82.5)                            | 157 (86.7)                             | 79 (88.8)                           | 525 (82.4)                         |
| Oxycodone HCl                          | 69 (37.5)                            | 91 (49.7)                             | 112 (61.9)                             | 60 (67.4)                           | 332 (52.1)                         |
| Other                                  | 1 (0.5)                              | 0                                     | 0                                      | 0                                   | 1 (0.2)                            |
| Within first 48 hours after dosing     | 140 (76.1)                           | 153 (83.6)                            | 160 (88.4)                             | 79 (88.8)                           | 532 (83.5)                         |
| Acetaminophen                          | 138 (75.0)                           | 151 (82.5)                            | 159 (87.8)                             | 79 (88.8)                           | 527 (82.7)                         |
| Oxycodone HCl                          | 77 (41.8)                            | 100 (54.6)                            | 117 (64.6)                             | 62 (69.7)                           | 356 (55.9)                         |
| Other                                  | 1 (0.5)                              | 0                                     | 0                                      | 0                                   | 1 (0.2)                            |

Abbreviation: HCl –hydrochloride

Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 11-14.

### Time to First Rescue Use

Time to first rescue use is displayed in Table 13. The estimated median time to first rescue use in the E-58425 group was 4.16 hours which was later than the estimated median time in the other three treatment groups. The Cox regression analysis results displayed in Table 14 also indicated that there was a statistically significantly longer time to use of rescue medication in the E-58425 group compared to other groups.

**Table 13: Time to First Use of Rescue Medication: Quartiles of Distribution (Full Analysis Set)**

| Treatment Group | Percentile of Survival Distribution | Point Estimate | 95% CI          |
|-----------------|-------------------------------------|----------------|-----------------|
| E-58425         | 25                                  | 1.39           | [1.30 to 1.75]  |
|                 | 50                                  | 4.16           | [2.95 to 7.22]  |
|                 | 75                                  | 19.23          | [10.28 to .]    |
| Tramadol        | 25                                  | 1.27           | [1.17 to 1.40]  |
|                 | 50                                  | 2.15           | [1.73 to 3.20]  |
|                 | 75                                  | 7.78           | [5.15 to 12.58] |
| Celecoxib       | 25                                  | 1.23           | [1.17 to 1.32]  |
|                 | 50                                  | 2.14           | [1.65 to 3.08]  |
|                 | 75                                  | 8.19           | [5.05 to 9.68]  |
| Placebo         | 25                                  | 1.17           | [1.07 to 1.18]  |
|                 | 50                                  | 1.58           | [1.23 to 2.20]  |
|                 | 75                                  | 3.93           | [3.02 to 8.23]  |

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 11-16.

**Table 14: Time to First Use of Rescue Medication: Cox Regression Analysis (Full Analysis Set)**

| Variable                                   | Comparison           | P-Value | Hazard Ratios <sup>a,b</sup> | 95% CI           |
|--------------------------------------------|----------------------|---------|------------------------------|------------------|
| Time to first use of rescue medication (h) | E-58425 vs Tramadol  | 0.0042  | 0.714                        | [0.567 to 0.899] |
|                                            | E-58425 vs Celecoxib | 0.0003  | 0.657                        | [0.523 to 0.826] |
|                                            | E-58425 vs Placebo   | <0.0001 | 0.536                        | [0.406 to 0.709] |

<sup>a</sup> A hazard ratio of >1 means that subjects in the E-58425 group had a shorter time than subjects in the reference group.

<sup>b</sup> Cox proportional hazards regression adjusted for center and Baseline pain.

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 11-17.

### Time to Meaningful Pain Relief

As shown in Table 15, the estimated median time to meaningful PAR was 1.87 hours for the E-58425 group, compared with 2.75 hours for the tramadol group and 2.51 hours for the celecoxib group. The median time was not reached for the placebo group. The E-58425 group had shorter times to achieve each percentile than each of the other groups.

**Table 15: Time to Meaningful Pain Relief (Full Analysis Set)**

| Variable                           | Treatment Group | Percentile of Survival Distribution | Point Estimate | 95% CI         |
|------------------------------------|-----------------|-------------------------------------|----------------|----------------|
| Time to meaningful pain relief (h) | E-58425         | 25                                  | 1.03           | [0.94 to 1.17] |
|                                    |                 | 50                                  | 1.87           | [1.56 to 2.53] |
|                                    |                 | 75                                  | 5.78           | [3.15 to .]    |
|                                    | Tramadol        | 25                                  | 1.12           | [0.99 to 1.26] |
|                                    |                 | 50                                  | 2.75           | [1.96 to 3.42] |
|                                    |                 | 75                                  | 6.66           | [4.00 to .]    |
|                                    | Celecoxib       | 25                                  | 1.28           | [1.15 to 1.51] |
|                                    |                 | 50                                  | 2.51           | [1.96 to 6.50] |
|                                    |                 | 75                                  | 8.00           | [6.50 to .]    |
|                                    | Placebo         | 25                                  | 1.34           | [0.94 to 3.01] |
|                                    |                 | 50                                  | .              | [2.53 to .]    |
|                                    |                 | 75                                  | .              | [. to .]       |

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 14.2.15.1.

### Dose/Dose Response

There was no analysis of dose response planned and conducted on this study.

### Durability of Response and Persistence of Effect

This was a multiple dose study. The median time to intake of rescue medication in the E-58425 group was 4.16 hours, which was longer than the time in the placebo group (1.58 hours), the celecoxib group (2.14 hours), and the tramadol group (2.15 hours).

#### **Reviewer Comment:**

*Based on this study, the median time-to-rescue was about 4 hours, which is shorter than the proposed dosing interval of every 12 hours for E-58425. Information on the use of rescue is included in the proposed label to inform prescribers.*

### Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted on this study.

## 6.2. ESTEVE-SACO4-201

### 6.2.1. Study Design

#### Overview and Objective

The primary objective of this study was to establish the effective dose between four strengths of E-58425 for moderate to severe pain based on PI, TOTPAR, use of supplementary analgesic medication, time of onset of PAR, and overall assessment. The secondary objectives were to assess the efficacy and safety of E-58425. Furthermore, plasma levels of E-58425 (tramadol and celecoxib) were studied in a subgroup of patients at two study centers at 0, 2, and 6 hours after administration of the study medication or at the time the subject decided to withdraw from the study.

#### **Reviewer Comment:**

*ESTEVE-SACO4-201 was a Phase 2 dose finding study on postsurgical acute pain after oral surgical procedures involving extraction of two (ipsilateral) or more impacted third molars requiring bone removal. This study was a placebo-controlled, single dose study that provided the first set of efficacy data for use of E-58425 in acute pain, comparing different doses of the product with a formulation of tramadol marketed in Europe and placebo.*

*The Applicant included the Phase 2 Study ESTEVE-SACO4-201 in their efficacy assessment. However, we note the following limitations in the design of this study that made it inadequate to be considered for evaluation of efficacy of E-58425:*

- The primary endpoint, SPID 0-8, is not an appropriate endpoint to support the proposed indication of acute pain.*
- Study ESTEVE-SACO4-201 was a single-dose study.*

*Thus, limited conclusions could be drawn from Study ESTEVE-SACO4-201 regarding the efficacy of E-58425 for acute pain, and this study was not reviewed in detail for assessment of efficacy. In general, the results of this study did not raise any concern against the efficacy findings for Study ESETEV-SUSA-301.*

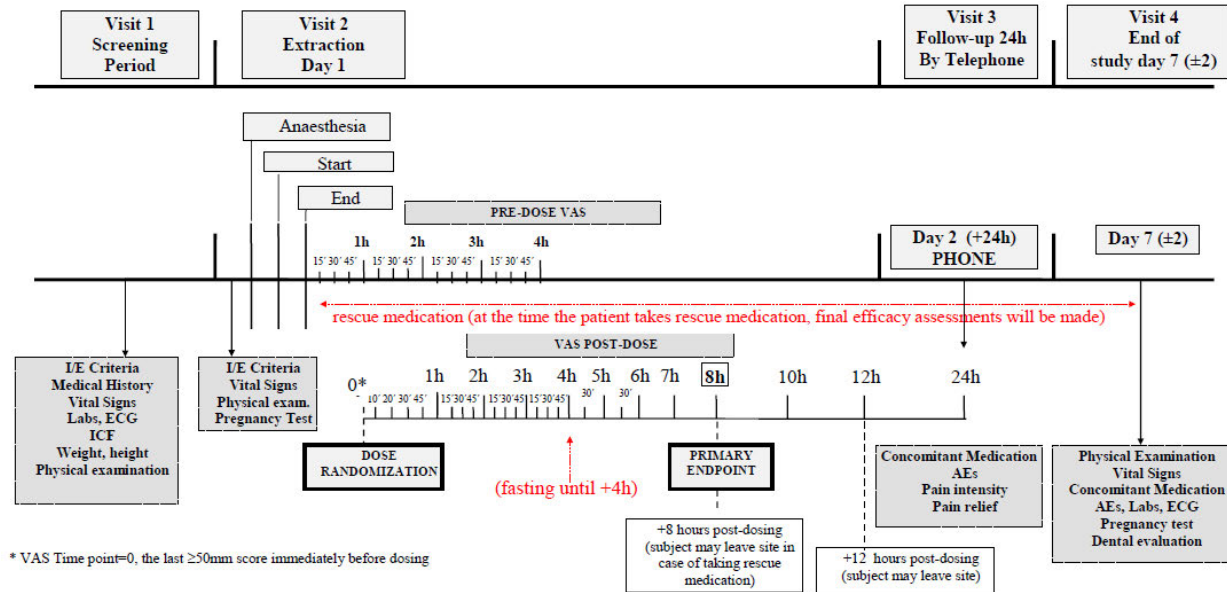
#### **Trial Design**

##### Basic Study Design

Study ESTEVE-SACO4-201 was a randomized, double-blind, active- (tramadol) and placebo--controlled, parallel group, single-dose, Phase 2, dose finding study in patients with moderate to severe pain dental pain after extraction of two or more impacted third molars requiring bone removal. This study was conducted using a standard design in accordance with the European Medicines Agency note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain (The European Agency for the Evaluation of Medicinal Products

May 2003). Figure 6 shows an overview of Study ESTEVE-SACO4-201.

**Figure 6: Overview of Study ESTEVE-SACO4-201**



Selected sites were to perform blood sampling at time points: 0, +2 and +6 hours post-dose for determination of plasma concentrations of E-58425 (Tramadol, M1 and celecoxib).

Abbreviations: VAS – visual analog scale, ECG – electrocardiogram, ICF – information consent form, AE – adverse event, I/E – Inclusion/Exclusion

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

The study consisted of three visits at the site and one telephone interview (a total of four visits): screening (Visit 1), dental extraction (Day 1, Visit 2), telephone interview (24-hour post-surgery follow-up, Visit 3), and final examination (Day 7, Visit 4).

After the dental extraction, the PI of the subject was assessed on a VAS at 15-minute intervals until a PI of 50 mm VAS was reached. If a subject did not reach the required PI within 4 hours after the dental procedure, he/she was excluded from the study.

Study treatment was administered as a single dose administration. After administration of the study medication, PI and PAR were assessed at several time points. The time to perceptible and meaningful PAR was assessed by stop watch. Patients were required to remain at the study site for 12 hours after the randomization (i.e., for a maximum of 16 hours after dental extraction).

At any time during the 12-hour observation period, the subject could choose to receive rescue medication. Current pain and PAR were assessed prior to the intake of rescue medication and stopped thereafter. Subjects taking rescue medication were asked to remain at the study site for 8 hours after randomization. The subject was to make an overall assessment of the study medication at the end of the 12-hour observation period or, if the subject withdrew prior to completing the observation period, at the time of withdrawal, or at the time of taking rescue

medication, whichever occurred first.

In a subgroup of subjects from two centers, a total of three blood samples (0, 2, and 6 hours postdosing or at the time of withdrawal) were collected to determine the plasma concentrations of E-58425.

Table 16 shows the schedule of assessments for Study ESTEVE-SACO4-201.

**Table 16: Schedule of Assessments for Study ESTEVE-SACO4-201**

|                                                                    | Visit 1<br>Screening<br>(-4 Weeks) | Visit 2<br>Day 1 | Visit 3<br>Day 2<br>(Telephone Contact<br>24 Hours After Dosing) | Visit 4<br>Day 7<br>(±2 Days) |
|--------------------------------------------------------------------|------------------------------------|------------------|------------------------------------------------------------------|-------------------------------|
| Written Informed Consent                                           | X                                  |                  |                                                                  |                               |
| Check of inclusion/exclusion criteria                              | X                                  | X                |                                                                  |                               |
| Demographic data, medical and dental history, etc.                 | X                                  |                  |                                                                  |                               |
| Body height and weight                                             | X                                  |                  |                                                                  |                               |
| Routine clinical laboratory                                        | X <sup>†</sup>                     |                  |                                                                  | X                             |
| ECG                                                                | X <sup>††</sup>                    |                  |                                                                  | X                             |
| For females: pregnancy test                                        |                                    | X                |                                                                  | X                             |
| General medical examination                                        | X                                  | X                |                                                                  | X                             |
| Vital signs                                                        | X                                  | X                |                                                                  | X                             |
| Impacted third molar extraction                                    |                                    | X                |                                                                  |                               |
| Randomization                                                      |                                    | X                |                                                                  |                               |
| Administration of test product                                     |                                    | X                |                                                                  |                               |
| Blood samples for determination of plasma concentration of E-58425 |                                    | X <sup>1</sup>   |                                                                  |                               |
| Documentation of adverse events                                    |                                    | X                | X                                                                | X                             |
| Previous and concomitant medication                                | X                                  | X                | X                                                                | X                             |
| Dental evaluation                                                  |                                    | X                |                                                                  | X                             |
| Pain intensity (VAS)                                               |                                    | X <sup>2</sup>   | X                                                                |                               |
| Pain relief (5-point ordinal scale)                                |                                    | X <sup>3</sup>   | X                                                                |                               |
| Time to perceptible and meaningful pain relief                     |                                    | X                |                                                                  |                               |

|  | Visit 1<br>Screening<br>(-4 Weeks) | Visit 2<br>Day 1 | Visit 3<br>Day 2<br>(Telephone Contact<br>24 Hours After Dosing) | Visit 4<br>Day 7<br>(±2 Days) |
|--|------------------------------------|------------------|------------------------------------------------------------------|-------------------------------|
|--|------------------------------------|------------------|------------------------------------------------------------------|-------------------------------|

Overall assessment of the study medication

X<sup>4</sup>

<sup>1</sup> Blood samples were to be taken in a subgroup of patients in at least one study center. Three blood samples of 4 mL were to be taken: 0, 2, and 6 hours post dose or at the time the patient decided to withdraw from the study. Vital signs assessments were to be reported before blood sampling.

<sup>2</sup> Pre-dose (every 15 minutes – or at the request of the subject – until a maximum of 4 hours post dental extraction: 15min, 30min, 45min, 1h, 1h 15min, 1h 30min, 1h 45min, 2h, 2h 15min, 2h 30min, 2h 45min, 3h, 3h 15min, 3h 30min, 3h 45 min, and 4h) and at 10min, 20min, 30min, 45min, 1h, 1h 15min, 1h 30min, 1h 45 min, 2h, 2h 15min, 2h 30min, 2h 45min, 3h, 3h 15min, 3h 30min, 3h 45min, 4h, 4h 30min, 5h, 5h 30min, 6h, 7h, 8h, 10h, 12h, and 24h after administration (or until rescue medication was taken).

<sup>3</sup> At 10min, 20min, 30min, 45min, 1h, 1h 15min, 1h 30min, 1h 45min, 2h, 2h 15min, 2h 30min, 2h 45min, 3h, 3h 15min, 3h 30min, 3h 45min, 4h, 4h 30min, 5h, 5h 30min, 6h, 7h, 8h, 10h, 12h, and 24h after administration.

<sup>4</sup> At the end of the 12-hour observation period or at the time of administration of rescue medication or at the time the patient decided to withdraw from the study before the 12h.

† Added in Amendment 2, amended protocol version 1.5.2 dated 28 January 2013: Routine clinical laboratory according to site practice was accepted from 15 days prior to Visit 1 Screening and until Visit 2 (before surgery).

†† Added in Amendment 2, amended protocol version 1.5.2 dated 28 January 2013: ECGs according to site practice were accepted from 15 days prior to Visit 1 Screening and until Visit 2 (before surgery).

Abbreviations: ECG – electrocardiogram, VAS – visual analog scale

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

## Study Location and Date

This study was conducted at nine centers in Spain. The first subject was screened on

(b) (6)

and the last subject completed the study on

(b) (6)

## Eligibility Criteria

Male and female subjects at least 18 years of age with moderate or severe pain after the extraction of at least two impacted third molars requiring bone removal were included in the study. Moderate to severe pain was defined as score of at least 50 mm on VAS. Subjects were excluded if they took any analgesic medication other than preoperative or intraoperative anesthetic agents within 12 hours before taking trial medication or after the dental surgical procedure.

## Dose Selection, Study Arms, and Randomization

Subjects who were eligible were randomly assigned to one of the following six treatment groups:

- Treatment 1: 1 tablet of E-58425 50 mg +1 tablet of placebo
- Treatment 2: 1 tablet of E-58425 100 mg +1 tablet of placebo
- Treatment 3: 1 tablet of E-58425 50 mg +1 tablet of E-58425 100 mg
- Treatment 4: 1 tablet of E-58425 100 mg +1 tablet of E-58425 100 mg
- Treatment 5: 2 capsules of tramadol 50 mg (Adolonta®)
- Treatment 6: 2 tablets of placebo

**Reviewer Comment:**

*Subjects in the tramadol group took Adolonta 100 mg as a single dose. The recommended dosing regimen for Ultram is 50 mg every 6 hours per its label. Additionally, Study ESTEVE-SACO4-201 did not include a celecoxib arm because celecoxib is not approved for treatment of acute pain in Europe.*

Duration of Treatment/Follow-Up

Study treatment was administered as a single dose administration. The study subjects stayed at the study site for 12 hours after the administration of study medication. They were followed up by a telephone interview 24-hour post-surgery and by a final examination 7 days after the surgery.

Rescue Medication

The Applicant did not mention the type or dosage of rescue medication in the study protocol.

**Study Endpoints**

The primary efficacy endpoint was the SPID from 0-8 hours. The PID was defined as below.

- $PID_t = PI_t - PI_0$ , where  $PI_0$  is the PI at  $t = 0$  hours and  $PI_t$  is the PI at specific time points. Positive values therefore correspond to an increase in pain, while negative values correspond to a decrease in pain.
- The SPID was defined as the sum of that PID between time 0 and time  $t$  weighted with the time between two consecutive values, i.e., each  $PID_t$  value was multiplied with the time interval since the previous evaluation and summed.

There were multiple secondary efficacy endpoints including the following:

- SPID from 0-12 hours
- PID at each time point
- PAR at each time point
- TOTPAR from 0-8 hours, where TOTPAR was defined as the sum of PAR between time 0 and time  $t$  weighted with the time between two consecutive values, i.e., each  $PAR_t$  value was multiplied with the time interval since the previous evaluation.
- TOTPAR from 0-12 hours
- Overall assessment of the study medication
- Rescue medication
- Rate of subjects with intake of at least one dose of rescue medication up to 8 and up to 12 hours after study drug administration
- Time to first intake of rescue medication
- Time to perceptible and meaningful PAR
- Responder rate with response defined as

- a 30% reduction in pain compared with baseline and a PI below 40 mm VAS;
  - a 50% reduction in pain compared with baseline and a PI below 40 mm VAS;
  - a 30% reduction in pain;
  - a 50% reduction in pain; or
  - a PI below 40 mm VAS.
- Time to response

Safety endpoints included laboratory results, ECG measurements, and AEs.

### Statistical Analysis Plan

The primary analysis endpoint was analyzed using an analysis of variance (ANOVA) model which included treatment and center effects and was to be performed to detect any global treatment or center effect. For the secondary efficacy endpoints SPID from 0-12 hours, PID at each time point, PAR at each time point, TOTPAR from 0-8 hours, and TOTPAR from 0-12 hours, the same ANOVA was applied as for the primary efficacy endpoint.

For subjects discontinued from the study, missing PI scores were imputed using the LOCF method. For subjects used rescue medication in the study, PI scores were only collected until rescue medication was taken and missing PI scores after rescue use were imputed using the LOCF method.

The overall assessment of the study medication was analyzed using the Cochran-Mantel-Haenszel test stratified by center to detect any treatment differences.

Rescue medication was analyzed as follows:

- The number of subjects that took at least one dose of rescue medication up to 8 and up to 12 hours after intake of study drug was compared between treatments using the Cochran-Mantel-Haenszel test stratified by center to detect any treatment differences.
- The time to first intake of rescue medication was analyzed using Kaplan-Meier estimates. The log-rank test was conducted to compare the median time to first intake of rescue medication.

The time to perceptible and time to meaningful PAR were analyzed using Kaplan-Meier curves and log-rank tests. The response rates at 8 and 12 hours were analyzed using the Cochran-Mantel-Haenszel test stratified by center. Time-to-response was analyzed as time-to-event data, taking the first time at which the response criterion was reached by each subject. Time-to-response was censored at the time of intake of rescue medication or at 12 hours in cases where the response criteria were not fulfilled.

Safety variables were analyzed descriptively.

### **Protocol Amendments**

There were two protocol amendments to the original protocol submission that included minor modifications. There were no significant changes to the safety measurements. The Applicant reported that both amendments were considered a non-substantial amendment per European Community Guideline 2010/C 82/01.

## **6.2.2. Study Results**

### **Compliance With Good Clinical Practices**

The Applicant stated that this study was performed in compliance with GCP, the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

### **Financial Disclosure**

Study ESTEVE-SACO4-201 was a Phase 2 dose finding study and was not considered a “covered clinical study.” The Applicant did not submit a Financial Disclosure for this study.

### **Patient Disposition**

The study was planned to include 360 subjects, 60 subjects per treatment group. A total of 334 subjects were randomized with the following number of subjects per treatment group: 55 in E-58425 50 mg, 53 in E-58425 100 mg, 57 in E-58425 150 mg, 57 in E-58425 200 mg, 58 in tramadol 100 mg, and 54 in the placebo group.

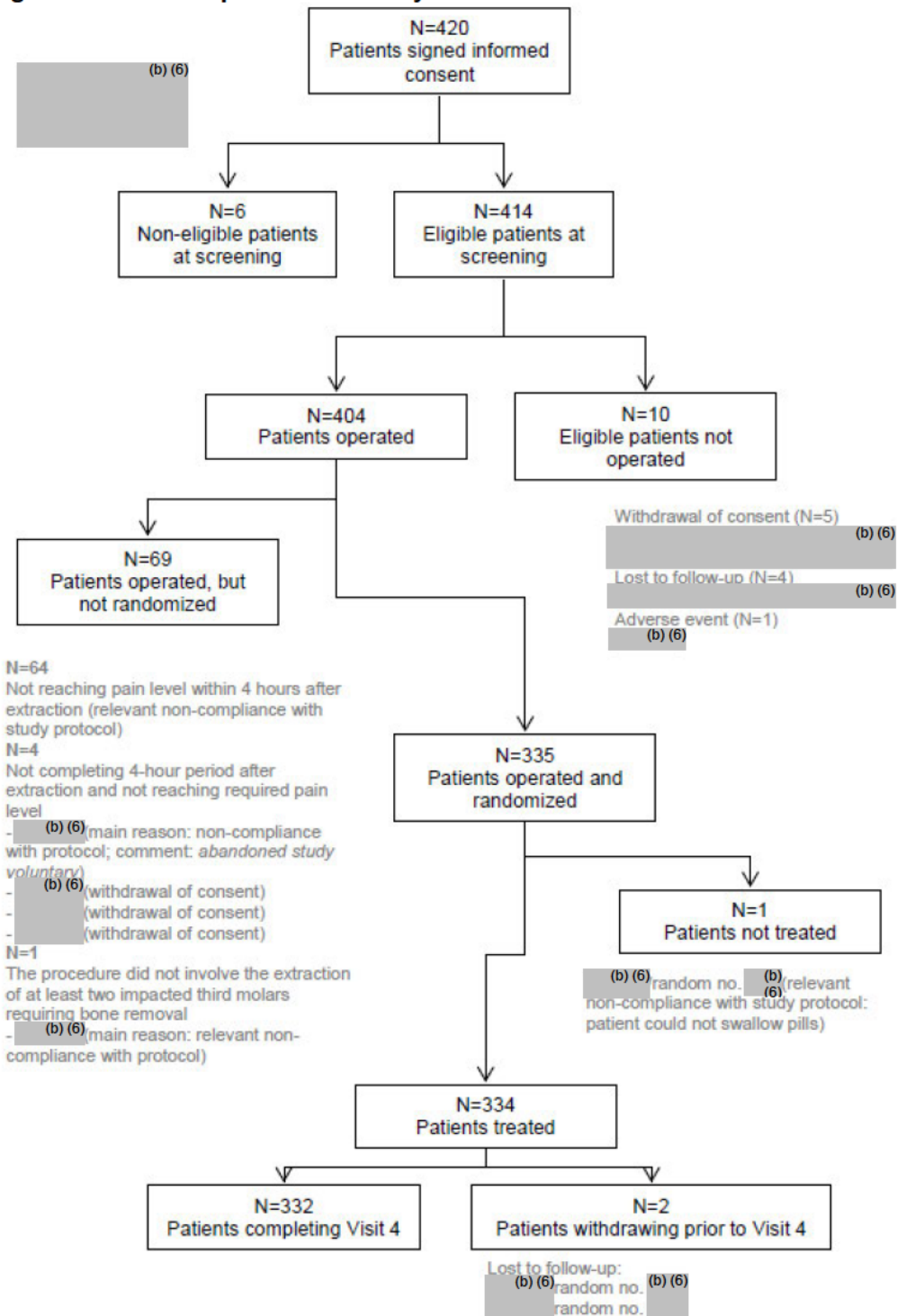
Definitions of the analysis sets used in this study are below:

- Safety analysis (SA) set: All subjects who were randomized and who received study medication (334).
- FA set: All subjects comprising the SA set for whom at least one valid VAS measurement was available after receiving the study medication (334).
- Per protocol (PP) set: All subjects of the FA set for whom no relevant protocol deviations were documented, at least three valid VAS measurements were available 8 hours after receiving the study medication, and who had not taken rescue medication during the first hour post-dose (228).

All randomized subjects (334) were included in the SA set and FA set. A total of 46 subjects were excluded from the PP set due to protocol deviations (see protocol deviations below for further detail). A total of 288 were included in PP set with the following number of subjects per treatment group: 45 in E-58425 50 mg, 47 in E-58425 100 mg, 54 in E-58425 150 mg, 46 in E-58425 200 mg, 49 in tramadol 100 mg, and 47 in the placebo group.

Figure 7 shows the patient disposition for Study ESTEVE-SACO-201.

**Figure 7: Patient Disposition for Study ESTEVE-SACO4-201**



Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

### Protocol Violations/Deviations

A total of 46 patients had major protocol deviations. The most frequent was the use of rescue medication during the first hour after administration of the study treatment (41 cases). Other protocol deviations included: violation of inclusion criterion #5: VAS score after dental extraction <50 mm (one case), violation of exclusion criterion #8: use of selective serotonin reuptake inhibitor or other antidepressant medication (two cases), violation against allowed time window ( $\leq 15$  min) between first predose PI measurement of  $\geq 50$  mm VAS and intake of study medication (one case), and deviation from planned dosing regimen (one case).

#### **Reviewer Comment:**

*A total of 334 subjects took study medication (including tramadol and placebo) and were included in the SA set and FA set. There were 53 to 58 subjects in each treatment group. A total of 46 of these subjects were excluded due to protocol deviations, mainly due to early intake of rescue medication. The remaining 288 subjects were included in the PP set (45 to 54 in different groups). The protocol deviations affected a high number of subjects relative to the total study population (46 out of 334, 13.7%). However, the data from this study were mainly used for safety analysis in this NDA review, and the SA set included all 334 subjects who took any study medication.*

### Table of Demographic Characteristics

A total of 142 (42.5%) male and 192 (57.5%) female subjects were included in the SA and FA set. A total of 327 subjects were Caucasian, and 7 subjects were not Caucasian. The subjects were 24.5 years old on average with an age range between 18 and 48 years. Subjects had a mean weight of 67.51 kg and a mean BMI of 23.50 kg/m<sup>2</sup>. No significant differences between treatments were observed for demographic parameters that would affect the safety analysis. Table 17 shows demographic characteristics of Study ESTEVE-SACO4-201.

Clinical Review  
NDA 213426  
E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

**Table 17: Demographic Characteristics of Study ESTEVE-SACO4-201**

|                                                                     | 50mg<br>E-58425<br>(N=55) | 100mg<br>E-58425<br>(N=53) | 150mg<br>E-58425<br>(N=57) | 200mg<br>E-58425<br>(N=57) | 100mg<br>Tramadol<br>(N=58) | Placebo<br>(N=54) | Total<br>(N=334) | p-value             |
|---------------------------------------------------------------------|---------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|-------------------|------------------|---------------------|
| <b>Sex [number of patients (%)]</b>                                 |                           |                            |                            |                            |                             |                   |                  |                     |
| Male                                                                | 31 (56.4)                 | 23 (43.4)                  | 25 (43.9)                  | 23 (40.4)                  | 26 (44.8)                   | 14 (25.9)         | 142 (42.5)       | 0.063 <sup>2</sup>  |
| Female                                                              | 24 (43.6)                 | 30 (56.6)                  | 32 (56.1)                  | 34 (59.6)                  | 32 (55.2)                   | 40 (74.1)         | 192 (57.5)       |                     |
| <b>Ethnic group [number of patients (%)]</b>                        |                           |                            |                            |                            |                             |                   |                  |                     |
| CAU                                                                 | 54 (98.2)                 | 51 (96.2)                  | 56 (98.2)                  | 56 (98.2)                  | 57 (98.3)                   | 53 (98.1)         | 327 (97.9)       | 0.942 <sup>2</sup>  |
| Other                                                               | 1 (1.8)                   | 2 (3.8)                    | 1 (1.8)                    | 1 (1.8)                    | 1 (1.7)                     | 1 (1.9)           | 7 (2.1)          |                     |
| <b>Age at the time of signing the informed consent form [years]</b> |                           |                            |                            |                            |                             |                   |                  |                     |
| Mean                                                                | 25.2                      | 25.1                       | 24.8                       | 23.7                       | 24.9                        | 23.3              | 24.5             | 0.317 <sup>1</sup>  |
| Median                                                              | 24.0                      | 23.0                       | 24.0                       | 22.0                       | 23.5                        | 22.0              | 23.0             |                     |
| SD                                                                  | 5.78                      | 5.62                       | 5.68                       | 6.17                       | 5.57                        | 4.80              | 5.63             | 0.0027 <sup>3</sup> |
| Min-Max                                                             | 18-45                     | 18-38                      | 18-42                      | 18-48                      | 18-44                       | 18-39             | 18-48            |                     |
| n                                                                   | 55                        | 53                         | 57                         | 57                         | 58                          | 54                | 334              |                     |
| <b>Height [cm]</b>                                                  |                           |                            |                            |                            |                             |                   |                  |                     |
| Mean                                                                | 171.1                     | 168.1                      | 170.1                      | 168.5                      | 168.4                       | 168.4             | 169.1            | 0.483 <sup>1</sup>  |
| Median                                                              | 171.0                     | 167.0                      | 170.0                      | 168.0                      | 169.5                       | 168.0             | 169.0            |                     |
| SD                                                                  | 8.59                      | 9.36                       | 8.56                       | 9.52                       | 10.45                       | 8.87              | 9.26             | 0.5127 <sup>3</sup> |
| Min-Max                                                             | 155-189                   | 149-196                    | 154-189                    | 149-192                    | 144-192                     | 153-187           | 144-196          |                     |
| n                                                                   | 55                        | 53                         | 57                         | 56                         | 58                          | 53                | 332              |                     |
| <b>Body weight [kg]</b>                                             |                           |                            |                            |                            |                             |                   |                  |                     |
| Mean                                                                | 72.31                     | 66.48                      | 69.23                      | 63.53                      | 67.47                       | 66.01             | 67.51            | 0.023 <sup>1</sup>  |
| Median                                                              | 70.00                     | 65.00                      | 66.65                      | 62.00                      | 65.60                       | 62.60             | 65.00            |                     |
| SD                                                                  | 13.582                    | 12.142                     | 13.856                     | 11.820                     | 14.562                      | 15.078            | 13.742           | 0.0636 <sup>3</sup> |
| Min-Max                                                             | 45.2- 103.0               | 47.5-106.3                 | 48.0-105.0                 | 42.0-104.3                 | 44.9-104.0                  | 44.1-104.0        | 42.0-106.3       |                     |
| n                                                                   | 55                        | 53                         | 57                         | 56                         | 58                          | 53                | 332              |                     |
| <b>BMI [kg/m<sup>2</sup>]</b>                                       |                           |                            |                            |                            |                             |                   |                  |                     |
| Mean                                                                | 24.62                     | 23.48                      | 23.78                      | 22.29                      | 23.61                       | 23.19             | 23.50            | 0.059 <sup>1</sup>  |
| Median                                                              | 24.30                     | 23.03                      | 22.66                      | 21.94                      | 23.19                       | 21.53             | 22.83            |                     |
| SD                                                                  | 3.885                     | 3.459                      | 3.716                      | 3.199                      | 3.550                       | 4.761             | 3.821            | 0.0592 <sup>3</sup> |
| Min-Max                                                             | 18.2- 35.6                | 17.4-36.8                  | 17.6-33.5                  | 16.7-36.5                  | 16.3-34.2                   | 17.6- 34.9        | 16.3-36.8        |                     |
| n                                                                   | 55                        | 53                         | 56                         | 56                         | 58                          | 53                | 331              |                     |

<sup>1</sup> p-value for treatment from ANOVA with factors treatment and center without interaction

<sup>2</sup> p-value for treatment from Cochran-Mantel-Haenszel test stratified by center

<sup>3</sup> p-value for center from ANOVA with factors treatment and center without interaction

Abbreviations: BMI – body mass index; CAU – Caucasian

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

### **Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

The study subjects were in good physical health and were not on any analgesic medication during the study except the reported study treatment or rescue medication.

### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

The study personnel administered the study medication as a single dose administration. There were no significant differences between treatment arms.

Ondansetron (intravenous or intramuscular) was permitted to treat the AEs of nausea or vomiting.

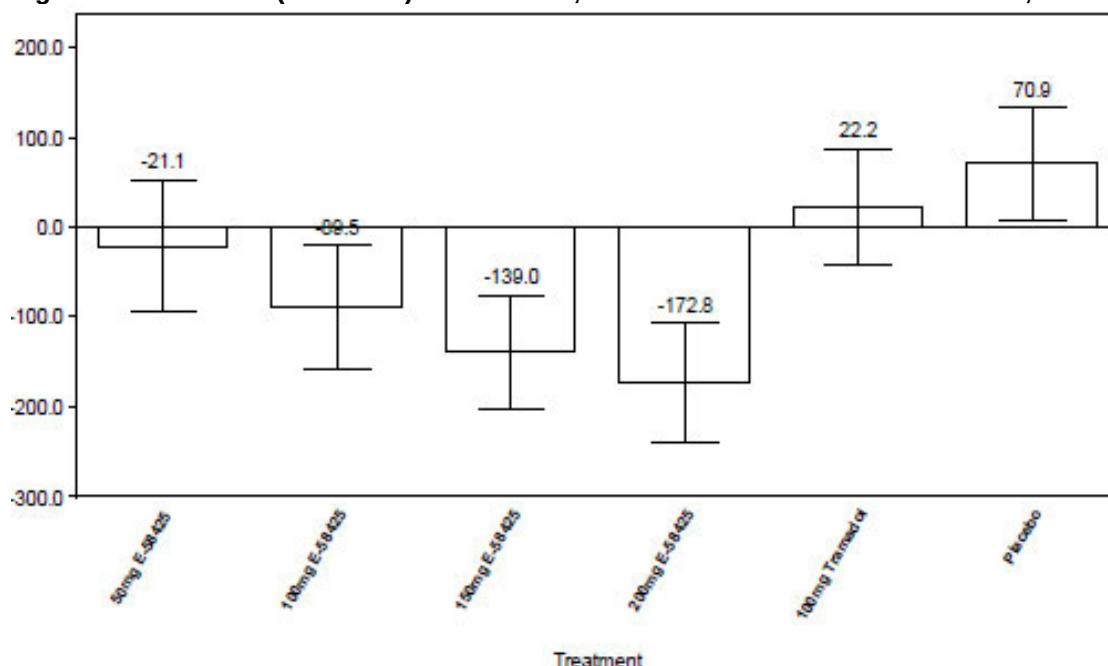
Rescue medication was analyzed as below:

1. The number of subjects that took at least one dose of rescue medication up to 8 and up to 12 hours after intake of study drug was compared between treatments using the Cochran-Mantel-Haenszel test stratified by center to detect any treatment differences.
2. The time to first intake of rescue medication was analyzed using Kaplan-Meier estimates. Comparison of the median time to first intake of rescue medication was performed using the log-rank test. If no rescue medication had been administered, the time to intake of rescue medication was censored with the time of completion (i.e., 12 hours post-dose), withdrawal, or drop out.

### **Efficacy Results – Primary Endpoint**

Study subjects in E-58425 groups experienced decrease in pain that was dose dependent. E-58425 50, 100, 150, and 200 mg led to a mean SPID 8 of -21.05, -89.53, -139.04, and -172.82 h\*mm, respectively, with negative values indicating a decrease in pain. Tramadol 100 mg and placebo led to an increase in pain (SPID: 22.16 and 70.91 h\*mm, respectively). See Figure 8 for a graphic presentation and Table 18 for descriptive statistics of the primary endpoint (SPID 8).

**Figure 8: Mean SPID (0-8 hours) With 95% CI, Last-Observation-Carried-Forward, PP Set<sup>a</sup>**



<sup>a</sup> Graph of means by treatment (mean  $\pm$  95% CI) PARAM = SPID (0-8h) [h\*mm]

Abbreviations: SPID – sum of pain intensity difference

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

**Table 18: SPID (0-8 hours), Last-Observation-Carried-Forward, PP Set**

|        | 50mg<br>E-58425<br>(N=45) | 100mg<br>E-58425<br>(N=47) | 150mg<br>E-58425<br>(N=54) | 200mg<br>E-58425<br>(N=46) | 100mg<br>Tramadol<br>(N=49) | Placebo<br>(N=47) | p-value             |
|--------|---------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|-------------------|---------------------|
| Mean   | -21.05                    | -89.53                     | -139.04                    | -172.82                    | 22.16                       | 70.91             | <0.001 <sup>1</sup> |
| Median | 22.30                     | -50.92                     | -187.54                    | -219.54                    | 73.33                       | 99.58             | 0.4712 <sup>2</sup> |
| SD     | 242.985                   | 233.626                    | 226.775                    | 224.241                    | 228.242                     | 212.612           |                     |
| Min    | -760.5                    | -516.3                     | -662.8                     | -486.2                     | -506.9                      | -396.4            |                     |
| Max    | 356.0                     | 329.2                      | 318.3                      | 320.7                      | 366.4                       | 359.7             |                     |
| n      | 45                        | 47                         | 54                         | 46                         | 49                          | 47                |                     |

<sup>1</sup> p-value for treatment from ANOVA with factors treatment and center without interaction

<sup>2</sup> p-value for center

Abbreviation: SPID – sum of pain intensity difference

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201 ("Section 14.3.1.2.2")

The Applicant used the LOCF method to impute PI scores after rescue use. For any subject using rescue medications, the PI score collected prior to the rescue use was carried forward until Hour 8. The PI prior to the rescue use may be larger than the PI at baseline and there was a high percentage of subjects using rescue medications in the tramadol 100 mg (74%) and placebo group (81%), which may account for the positive SPID8 in these two groups.

The study provides some support for a dose-response relationship for E-58425 and does not contradict the findings in Study ESTEVE-SUSA-301.

### **Data Quality and Integrity**

This study was started before December 17, 2016 and legacy data were used to create the analysis dataset model (ADaM) data for the integrated analyses.

As part of the filing review, it was noted that the narratives of SAEs in section 12.3.2 lack adequate detail. On July 23, 2019, inadequacy of narratives of SAEs was communicated with the Applicant in the “filing communication - Filing review issues identified” letter. On August 2, 2019, the Applicant provided additional information in response to the Division’s request.

#### **Reviewer Comment:**

*The Applicant’s response to the Division’s request was adequate. There were no other significant issues concerning the submitted data quality or integrity for this study.*

### **Efficacy Results – Secondary and Other Relevant Endpoints**

In general, efficacy results from secondary endpoints supported the efficacy results that were seen with the primary endpoint. Given that Study ESTEVE-SACO4-201 was a dose finding study using a single dose of study medication, this review does not include further analysis of efficacy results for secondary endpoints.

### **Dose/Dose Response**

In this single dose study, the higher doses of E-58425 (100, 150, and 200 mg) had a greater effect on SPID and TOTPAR compared with 100 mg tramadol and placebo. The subjects who received the highest doses of E-58425 (150 mg and 200 mg) required lower amount of rescue medication and showed longer mean times to intake of rescue medication compared with the tramadol 100 mg and placebo groups.

The lowest dose of E-58425 (50 mg) did not show any superior efficacy compared with tramadol 100 mg and placebo.

### **Durability of Response and Persistence of Effect**

This was a single dose study. The mean times to intake of rescue medication in E-58425 treatment groups 50, 100, 150, and 200 mg were 4.4, 6.1, 6.9, and 7.5 hours, respectively. The times to intake of rescue medication in the higher dose groups were longer than the time in the placebo group (2.8 hours) and the tramadol 100 mg tramadol group (4.4 hours).

#### **Reviewer Comment:**

*Based on this study, the time-to-rescue was 7 to 8 hours, which is shorter than the proposed dosing regimen of every 12 hours for E-58425.*

### **Additional Analyses Conducted on the Individual Trial**

No additional analyses were conducted for this study.

## **7. Integrated Review of Effectiveness**

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### **7.1. Assessment of Efficacy Across Trials**

Not applicable. The Applicant performed a single trial (Phase 3 factorial study (ESTEVE-SUSA-301)) to support the efficacy of the product.

### **7.2. Additional Efficacy Considerations**

#### **7.2.1. Considerations on Benefit in the Postmarket Setting**

There are no clinically important differences in how the drug was studied in the Phase 3 factorial study (ESTEVE-SUSA-301) and how the drug may be used in the postmarket setting.

#### **7.2.2. Other Relevant Benefits**

The proposed dosing regimen for E-58425 is 2 tablets every 12 hours as needed for PAR. This dosing regimen provides a more convenient dosing schedule compared with other short acting opioid products that require more frequent dosing.

### **7.3. Integrated Assessment of Effectiveness**

The Applicant provided substantial evidence in support of the effectiveness of E-58425 for the proposed indication of management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

E-58425 is a fixed-dose combination product containing two established analgesics, celecoxib and tramadol, with different mechanisms of action. As a 505(b)(2) application, the Applicant relied in part on FDA's findings of safety and efficacy for Celebrex and Ultram as well as original studies performed by the Applicant. The Applicant performed Phase 1 studies in healthy volunteers that provided BA bridging data for reliance upon FDA's finding of safety and effectiveness of the RLDs, Celebrex and Ultram.

The Applicant performed one Phase 3 factorial study (ESTEVE-SUSA-301) designed to fulfill the requirements for fixed-combination prescription drugs under 21 CFR 300.50 of the Federal Food, Drug and Cosmetic Act. Refer to Section 6.1 for details of efficacy results for Study

ESTEVE-SUSA-301. The study was designed to demonstrate that each component of E-58425 contributes to the efficacy of the product and that E-58425 is superior to placebo. The Phase 3 study was performed in patients who had moderate to severe pain after bunionectomy. Postoperative acute pain is one of the pain models that is commonly used in clinical trials for analgesic drug development programs for acute pain. The Phase 3 factorial study demonstrated statistically significant superior efficacy of E-58425 over placebo, and that each component of E-58425 contributed to the efficacy of the product for the proposed indication of management of acute moderate to severe pain.

## 8. Review of Safety

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### 8.1. Safety Review Approach

The two active ingredients in the proposed product, celecoxib and tramadol, have been widely used in the United States since the times of their approval (1998 and 1995, respectively). The Applicant submitted a 505(b)(2) application that relies in part on FDA's finding of safety for Celebrex and Ultram as individual components. The Applicant did not perform specific safety studies, but they collected safety data in all of their clinical studies. The safety review includes review of all seven clinical studies submitted to this NDA: refer to Table 1 and Table 2 in Section 5.1 for the list of the clinical studies reviewed. Given the differences in study designs, objectives, populations (healthy volunteers versus patients), and drug dosing regimens, the data from clinical studies are analyzed in different groups as shown below:

- Phase 1 studies in healthy volunteers (four single dose studies and one multiple dose study)
- Phase 2 single dose, dose-finding study in patients with moderate to severe pain
- Phase 3 multiple dose, factorial study in patients with moderate to severe pain

The clinical studies that were performed by MRL for the development of celecoxib and tramadol tablet outside the United States are not part of this NDA submission. The SAEs that occurred during MRL studies are included in the safety review.

Additionally, postmarket safety data are reviewed for possible interactions when celecoxib and tramadol are used concomitantly. Refer to Section 8.9 for details.

### 8.2. Review of the Safety Database

#### 8.2.1. Overall Exposure

A total of 550 subjects received at least one dose of E-58425 at any dose including 145 healthy volunteers in Phase 1 studies (E-58425 200 mg), 222 subjects in the Phase 2 dose finding study,

and 183 subjects in the Phase 3 factorial study. Of the 550 subjects who were exposed to E-58425, 385 subjects received E-58425 200 mg, which is the dose proposed for marketing, and 165 received lower doses. Table 19 shows the cumulative subject exposure for the safety population, including treatment and placebo groups.

**Table 19: Cumulative Subject Exposure for Safety Population**

| Safety Database for the E-58425<br>Individuals Exposed to any Treatment in This NDA (N <sup>1</sup> =1123) |                      |                       |                          |                        |                         |                          |                                            |                 |
|------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|--------------------------|------------------------|-------------------------|--------------------------|--------------------------------------------|-----------------|
| Clinical Trial Groups                                                                                      | E-58425 50 mg (n=55) | E-58425 100 mg (n=53) | Co-crystal 150 mg (n=57) | E-58425 200 mg (n=385) | Tramadol 100 mg (n=338) | Celecoxib 100 mg (n=279) | Tramadol 100 mg + Celecoxib 100 mg (n=106) | Placebo (n=143) |
| Healthy volunteers: Five Phase 1 studies (N=152)                                                           | 0                    | 0                     | 0                        | 145                    | 97                      | 97                       | 106                                        | 0               |
| Dose finding study: ESTEVE-SACO4-201 (N=334)                                                               | 55                   | 53                    | 57                       | 57                     | 58                      | 0                        | 0                                          | 54              |
| Controlled trial: ESTEVE-SUSA-301 (N=637)                                                                  | 0                    | 0                     | 0                        | 183                    | 183                     | 182                      | 0                                          | 89              |

N<sup>1</sup> = Total number of subjects who were included in the clinical studies under NDA 213426. Note that all Phase 1 studies were cross-over design and subjects received more than one treatment.

Source: Reviewer-generated based on the Applicant's submission, Table 2.7.4-3

## 8.2.2. Relevant Characteristics of the Safety Population

Demographics and baseline characteristics of treatment groups in the controlled studies ESTEVE-SUSA-301 and ESTEVE-SACO4-201 are discussed in Section 6.1 (Table 7) and Section 6.2 (Table 17), respectively. There were no significant differences between treatment groups.

## 8.2.3. Adequacy of the Safety Database

The safety database was adequate for the target population of acute pain patients. A total of 183 patients received the proposed dose of E-58425 200 mg every 12 hours for 48 hours in the Phase 3 factorial study for pain after bunionectomy. A total of 57 patients received the E-58425 200 mg as a single dose treatment in the Phase 2 dose finding study for pain after dental surgery. The longest duration of exposure to E-58425 at proposed dose of 200 mg twice per day was 7.5 days, in the Phase 1 multiple dose study in healthy volunteers (32 healthy volunteers were included in the cross-over study and 29 of them received E-58425 200 mg).

Given the available safety data for celecoxib and tramadol individually, and the available data from the studies performed by the Applicant for the combination of celecoxib and tramadol, tablet, there are adequate safety data to inform the safety of the product. The data were collected in patients that are generalizable to the U.S. target population.

### **8.3. Adequacy of Applicant's Clinical Safety Assessments**

#### **8.3.1. Issues Regarding Data Integrity and Submission Quality**

The clinical data from studies started after December 17, 2016, were in conformance with the required data standards specified in the FDA Data Standards Catalog and the Technical Rejection Criteria for Study Data Document. The two clinical studies conducted under IND 128177, ESTEVE-SUSA-101 and ESTEVE-SUSA-301, started after this deadline and fulfill the standards. The analysis files for these studies were derived from the study data tabulation model files (version 3.2), which were prepared from case report form data. No non-study data tabulation model data were used to create the ADaM data from these studies (ADaM version 1.0 and 2.1, respectively).

For the clinical data from studies started before December 17, 2016, legacy data were used to create the ADaM for the integrated analyses. These studies included ESTEVE-SACO4-103, ESTEVE-SACO4-102, ESTEVE-SACO4-104, ESTEVE-SACO4-105, and ESTEVE-SACO4-201.

The following issues were identified during the safety review:

- Some of the reference documents such as case report forms did not open through the provided link in Define.xml due to incorrect file names. These documents were searchable through case report forms, but it was time consuming.
- The narratives of SAEs did not include adequate details. This issue was communicated with the Applicant. The Applicant provided adequate additional information. Refer to Section 6.2.2 for details.

There were no other important issues regarding data quality or the quality of the overall submission that affected the safety review.

#### **8.3.2. Categorization of Adverse Events**

The Applicant's definitions of TEAEs and SAEs were acceptable. For the purposes of pooling, the Applicant coded AEs using the Medical Dictionary for Regulatory Activities version 12.1 for Studies ESTEVE-SACO4-103 and ESTEVE-SACO4-102, version 13.1 for Study ESTEVE-SACO4-104, version 16.1 for Study ESTEVE-SACO4-105, version 15.1 for Study ESTEVE-SACO4-201, version 19.0 for Study ESTEVE-SUSA-101, and version 19.1 for Study ESTEVE-SUSA-301. The Applicant

harmonized the coding of AEs in the integrated summary of safety with Medical Dictionary for Regulatory Activities version 20.1.

### 8.3.3. Routine Clinical Tests

The methodology and frequency of routine clinical testing were adequate for clinical studies under this NDA. For Study ESTEVE-SUSA-301, routine clinical tests such as vital signs, physical exam, and ECGs were performed at appropriate intervals. Additionally, the following clinical laboratory tests were performed for Study ESTEVE-SUSA-301 at screening, before the first dose of study medication on Day 1, before discharge from the study center, and at follow-up:

- Hematology: hemoglobin, hematocrit, platelet count (or estimate), red blood cell count, white blood cell count (including differential)
- Serum chemistry: glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, sodium, potassium, calcium, chloride, bicarbonate, lactate dehydrogenase, albumin
- Urinalysis (dipstick): pH, specific gravity, blood, glucose, protein, ketones, nitrate, leukocytes

Similarly, the methodology and frequency of routine clinical testing were adequate for Study ESTEVE-SACO4-201 after dental surgery and for Phase 1 studies in healthy volunteers. Refer to Table 16 for the schedule of assessments for study ESTEVE-SACO4-201. Refer to Section 8.4 for details of the results of safety assessments.

## 8.4. Safety Results

### 8.4.1. Deaths

There were no deaths in any of the clinical studies during the development program for E-58425.

### 8.4.2. Serious Adverse Events

There were no SAEs in healthy volunteers in any of the Phase 1 studies, including the Phase 1 study that was performed by MRL outside the U.S. There were no SAEs in the Phase 3 Study ESTEVE-SUSA-301.

There were five SAEs in four patients in Phase 2 Study ESTEVE-SACO4-201 that required hospitalization of patients, including the following (SAEs are underlined):

1. Postoperative abscess in one patient in the E-58425 50 mg group
- 2.-3. Inflammation and infection (two SAEs) in one patient in the E-58425 150 mg group

4. Nausea in one patient in the E-58425 200 mg group
5. Vomiting in one patient in tramadol 100 mg group

Study ESTEVE-SACO4-201 was a single dose study and there were no study discontinuations due to AEs.

During the three clinical studies that were performed by MRL outside the United States (Europe and Canada), there were no SAEs in the Phase 1 study. There were 16 SAEs in 13 patients in the Phase 3 studies, including 2 SAEs in Study MR308-3501 and 14 SAEs in Study MR308-3502 including the following (SAEs are underlined). Note that E-58425 is referred to as MR308 in MRL studies.

SAEs in Study MR308-3501 after dental surgery:

1. Vomiting in tramadol 100 mg QID (four times daily) group
2. Local infection in MR308 200 mg BID (twice daily) group

SAEs in Study MR308-3502 after abdominal hysterectomy:

3. Deep vein thrombosis in the tramadol 100 mg QID group
- 4.-5. Gastritis and pulmonary embolism in the tramadol 100 mg QID group
6. "Subileus" in the tramadol 100 mg QID group
7. Renal colic in the celecoxib 100 mg BID group
8. Intestinal obstruction in the celecoxib 100 mg BID group
9. Hematoma in the celecoxib 100 mg BID group
10. Ileus in the MR308 100 mg BID group
- 11.-12. Abdominal wall abscess (intra-abdominal hematoma) and pyrexia in the MR308 100 mg BID group
13. Extravasation of blood in the MR308 150 mg BID group
14. Vomiting in the MR308 150 mg BID group
- 15.-16. Hematoma and aponeurosis contusion in the MR308 150 mg BID group

The Applicant assessed events of hematoma (SAE #9 with celecoxib) and extravasation of blood (SAE #13 with MR308 150 mg) as suspected unexpected serious adverse reactions. The Applicant considered both events to be more likely "a complication of the concomitant treatment with the low molecular weight heparin."

**Reviewer Comments:**

*The Applicant reported a total of four SAEs of hematoma/bleeding including hematoma with celecoxib 100 mg BID (SAE #9) and extravasation of blood with MR308 150 mg BID (SAE #13), abdominal wall abscess (intra-abdominal hematoma) with MR308 150 mg BID (SAE #11), and hematoma with MR308 150 mg BID (SAE #15). From the four SAEs of hematoma/bleeding in study MR301-3502, one was in the celecoxib group and three were in the MR308 group. Study*

*MR308-3502 was performed in patients who underwent abdominal hysterectomy. Study subjects received low molecular weight heparin for deep vein thrombosis prophylaxis. Bleeding is a common adverse drug reaction with low molecular weight heparin and the risk of bleeding is higher with concomitant use of anticoagulants including NSAIDs, as it is described in the label for Lovenox® (enoxaparin, low molecular weight heparin). The SAEs of hematoma and bleeding occurred in four subjects out of a total of 1,138 subjects who were enrolled in study MR308.3502. The reported SAEs of hematoma and bleeding are likely related to concomitant use of low molecular weight heparin and do not raise a new safety concern.*

*In general, a total of 21 SAEs were reported in 17 subjects from a pool of more than 2,000 subjects who received E-58425, including studies that were performed by MRL outside the United States. There were no SAEs reported in subjects in the placebo groups, including 143 subjects in studies performed by the Applicant and more than 200 subjects in studies performed by MRL. Review of SAEs does not raise any new safety concerns that are not included in the labeling for Celebrex and Ultram.*

#### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Two subjects (1.4%) withdrew from the Phase 1 studies. There were no AEs that led to study discontinuation in the single-dose Phase 2 study. Six subjects withdrew from the Phase 3 study due to AEs, three subjects (1.6%) in each tramadol and E-58425 treatment groups. Discontinuation due to AEs are shown in Table 20.

**Table 20: Discontinuations Due to Adverse Events**

| Subject #                             | Treatment             | AE Term                      |
|---------------------------------------|-----------------------|------------------------------|
| <b>Phase 1 Study ESTEVE-SACO4-103</b> |                       |                              |
| (b) (6)                               | E-58425 200 mg        | Vomiting                     |
| <b>Phase 1 Study ESTEVE-SACO4-102</b> |                       |                              |
| (b) (6)                               | Multiple <sup>1</sup> | Decreased hemoglobin level   |
| <b>Phase 3 Study ESTEVE-SUSA-301</b>  |                       |                              |
| (b) (6)                               | E-58425 200 mg        | Nausea                       |
|                                       | E-58425 200 mg        | Nausea                       |
|                                       | E-58425 200 mg        | Pruritus                     |
|                                       |                       | Rash                         |
|                                       | Tramadol 100 mg       | Emesis                       |
|                                       | Tramadol 100 mg       | Supraventricular tachycardia |
|                                       | Tramadol 100 mg       | Vomiting                     |

<sup>1</sup> Subject # (b) (6) in study ESTEVE-SACO4-102 was withdrawn before the last dosing. Subject had received three treatments including Celebrex 100 mg in period 1, Adolonta® 100 mg + Celebrex® 100 mg in period 2, and co-crystal 200 mg in period 3.

Abbreviations: AE – adverse event

Source: Reviewer-generated based on the Applicant's submission, Module 2.7 – Clinical Summary

#### **Reviewer Comments:**

*In general, the incidence of discontinuations due to AEs was similar between the tramadol group and the E-58425 group in the Phase 3 study. Nausea and vomiting were the most common*

*reason for study discontinuation due to AEs. Nausea resulted in study discontinuation in 1.1% of subjects in the E-58425 group and vomiting resulted in study discontinuation in 1.1% of subjects in the tramadol group. This is consistent with the Ultram label listing nausea and vomiting as common AEs. Pruritus and rash are also listed as common adverse reactions in Ultram and Celebrex's label, respectively. Risk of gastrointestinal bleeding is listed in warnings for Celebrex. The Applicant reported that low hemoglobin level in case #034 from Study ESTEVE-SACO4-102 was resolved at the end of study. Supraventricular tachycardia occurred in a 57-year-old white female after receiving three doses of tramadol 50 mg every 6 hours. The subject had a history of palpitations in relation with bleeding (i.e., menstrual cycles). The subject was treated with 6 mg IV adenosine. Tachycardia is listed in Ultram's label under section 6.1 as an adverse reaction with incidence of less than 1% that are possibly causally related.*

*In general, review of discontinued cases due to AEs did not raise any new safety concerns with the proposed product.*

#### **8.4.4. Significant Adverse Events**

Refer to Section 8.4.2 for Serious Adverse Events, Section 8.4.3 for Dropouts and/or Discontinuations Due to Adverse Effects, Section 8.4.5 for Treatment-Emergent Adverse Events and Adverse Reactions, and Section 8.4.6 for Laboratory Findings including marked hematological and other laboratory abnormalities. The Applicant did not report any other events that led to an intervention, including withdrawal of E-58425, dose reduction, or significant additional concomitant therapy other than those reported as SAEs in other sections.

In general, the type and severity of AEs that occurred in the E-58425 group were comparable to those that occurred in the tramadol group, with the most TEAEs occurring in the Gastrointestinal disorders SOC (nausea and vomiting) and Nervous system disorders SOC (dizziness and headache).

Additionally, the AEs were analyzed with a focus on common AE preferred terms (PTs) associated with opioid-related safety and compilation of abuse-related AE terms as recommended in the Agency's guidance, Assessment of Abuse Potential of Drugs (January 2017). The highest reported abuse-related AEs were dizziness and somnolence that occurred with similar incidence in the E-58425 200 mg group and tramadol group. Of note, in Study ESTEVE-SUSA-301 somnolence was reported with a slightly higher incidence in the E-58425 group (8.2%) compared with the tramadol group (5.5%). Because somnolence, sedation, and fatigue are all related to central nervous system (CNS) depression, they are presented together as shown in Table 21 to examine the overall effect by treatment group in Study ESTEVE-SUSA-301. This analysis showed more AEs related to CNS depression in the E-58425 group (8.7%) compared with the tramadol group (6%). Additionally, the PT asthenia (from SOC General disorders and administration site conditions, which was reported as weakness or decreased energy) had an incidence of 0.5% in the E-58425 group and 2.2% in the tramadol group. Taking

into consideration that the terms fatigue, weakness, and decreased energy may be used in similar contexts by patients in the clinical setting, the small difference in the incidence of PTs related to CNS depression did not seem to be clinically meaningful. Refer to Section 8.4.5 for further details.

**Table 21: TEAEs in Study ESTEVE-SUSA-301 by Preferred Terms Related to CNS Depression**

| <b>Preferred Term (PT)</b>           | <b>E-58425<br/>(N=183)<br/>n (%)</b> | <b>Tramadol<br/>(N=183)<br/>n (%)</b> | <b>Celecoxib<br/>(N=182)<br/>n (%)</b> | <b>Placebo<br/>(N=89)<br/>n (%)</b> |
|--------------------------------------|--------------------------------------|---------------------------------------|----------------------------------------|-------------------------------------|
| <b>PTs related to CNS depression</b> | 16 (8.7%)                            | 11 (6.0%)                             | 6 (3.3%)                               | 3 (3.4%)                            |
| Somnolence                           | 15 (8.2)                             | 10 (5.5)                              | 4 (2.2)                                | 3 (3.4)                             |
| Sedation                             | 0                                    | 1 (0.5)                               | 0                                      | 0                                   |
| Fatigue                              | 1 (0.5)                              | 0                                     | 2 (1.1)                                | 0                                   |
| Other                                |                                      |                                       |                                        |                                     |
| Asthenia                             | 1 (0.5)                              | 4 (2.2)                               | 0                                      | 0                                   |

Abbreviations: TEAE – Treatment-Emergent Adverse Event, PT – preferred term, CNS - central nervous system  
Source: Reviewer-generated, based on reported AEs of Study ESTEVE-SUSA-301

In general, the safety analysis of AEs for E-58425 was comparable to that for tramadol. There were no AEs that represented any new significant safety concern with E-58425.

#### 8.4.5. Treatment-Emergent Adverse Events and Adverse Reactions

TEAEs were analyzed in three groups of Phase 1 studies in healthy volunteers, Phase 2 single dose Study ESTEVE-SACO4-201 after dental surgery, and Phase 3 multiple dose Study ESTEVE-SUSA-301 after bunionectomy.

##### Treatment-Emergent Adverse Events in Phase 1 Studies

In the Phase 1 studies, 41.3% (78/189) of healthy volunteers in the E-58425 group experienced at least one TEAE, compared with 47.4% in the tramadol group, 24.7% in the celecoxib group, and 52.8% in the tramadol + celecoxib group. TEAEs were analyzed in two groups of healthy volunteers taking the treatment as single dose or multiple dose. A summary of number of subjects with at least one TEAE in Phase 1 studies is shown in Table 22. The incidence of TEAEs was lower in the celecoxib group compared with other treatment groups containing tramadol. The SOC Nervous system disorders and Gastrointestinal disorders had the highest number of events and the highest proportion of subjects with TEAEs in Phase 1 studies. For the SOC Nervous system disorders, the most commonly reported PTs were somnolence and dizziness. For the SOC Gastrointestinal disorders, the most commonly reported PTs were nausea and vomiting.

**Table 22: Summary of TEAEs in Phase 1 Studies**

|                                            | <b>E-58425</b>             |                             | <b>Tramadol</b>           |                             | <b>Celecoxib</b>          |                             | <b>Tramadol + Celecoxib</b> |                             |
|--------------------------------------------|----------------------------|-----------------------------|---------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------------|-----------------------------|
|                                            | <b>Single Dose (N=160)</b> | <b>Multiple Dose (N=29)</b> | <b>Single Dose (N=67)</b> | <b>Multiple Dose (N=30)</b> | <b>Single Dose (N=69)</b> | <b>Multiple Dose (N=28)</b> | <b>Single Dose (N=78)</b>   | <b>Multiple Dose (N=28)</b> |
| Number of AEs                              | 152                        | 31                          | 49                        | 57                          | 17                        | 13                          | 72                          | 52                          |
| Number of subjects with AEs (n (%))        | 65 (40.6%)                 | 13 (44.8%)                  | 20 (29.9%)                | 26 (86.7%)                  | 13 (18.8%)                | 11 (39.3%)                  | 36 (46.2%)                  | 20 (71.4%)                  |
| Number of severe AEs                       | 6                          | 1                           | 0                         | 2                           | 0                         | 0                           | 2                           | 4                           |
| Number of subjects with severe AEs (n (%)) | 4 (2.5%)                   | 1 (3.4%)                    | 0                         | 2 (6.7%)                    | 0                         | 0                           | 2 (2.6%)                    | 4 (14.3%)                   |

Abbreviations: TEAE – treatment-emergent adverse event, AE – adverse event  
Source: Reviewer-generated based on the Applicant's submission, ISS, Table 22

### Treatment-Emergent Adverse Events in Phase 2 Study

In the Phase 2 dose finding study (Study ESTEVE-SACO4-201), a total of 80 TEAEs were reported that were dependent on the dose of E-58425, ranging from 12.7%, 11.3%, 15.8%, to 29.8% with intake of E-58425 50 mg, 100 mg, 150 mg, and 200 mg, respectively. The TEAEs in the E-58425 200 mg (tramadol 88 mg) group (29.8%) were comparable with the TEAEs in the tramadol 100 mg group (29.3%). There were no TEAEs leading to study discontinuation. The most commonly reported TEAEs were Gastrointestinal disorders, including vomiting and nausea. Table 23 shows TEAEs in Study ESTEVE-SACO4-201 by SOC and PT.

**Table 23: TEAEs in Phase 2 Study ESTEVE-SACO4-201 by System Organ Class and Preferred Term**

|                                                 | <b>50 mg E-58425 (N=55)</b> | <b>100 mg E-58425 (N=53)</b> | <b>150 mg E-58425 (N=57)</b> | <b>200 mg E-58425 (N=57)</b> | <b>100 mg Tramadol (N=58)</b> | <b>Placebo (N=54)</b> | <b>Total (N=334)</b> |
|-------------------------------------------------|-----------------------------|------------------------------|------------------------------|------------------------------|-------------------------------|-----------------------|----------------------|
| <b>Number of Patients (%), Number of Events</b> |                             |                              |                              |                              |                               |                       |                      |
| <b>Gastrointestinal disorders</b>               |                             |                              |                              |                              |                               |                       |                      |
| All                                             | 1 (1.8), 1                  | 3 (5.7), 3                   | 2 (3.5), 2                   | 7 (12.3), 10                 | 7 (12.1), 10                  | 0 (0.0), 0            | 20 (6.0), 26         |
| Vomiting                                        | 0 (0.0), 0                  | 2 (3.8), 2                   | 2 (3.5), 2                   | 5 (8.8), 5                   | 5 (8.6), 5                    | 0 (0.0), 0            | 14 (4.2), 14         |
| Nausea                                          | 0 (0.0), 0                  | 1 (1.9), 1                   | 0 (0.0), 0                   | 5 (8.8), 5                   | 4 (6.9), 4                    | 0 (0.0), 0            | 10 (3.0), 10         |
| Abdominal pain                                  | 0 (0.0), 0                  | 0 (0.0), 0                   | 0 (0.0), 0                   | 0 (0.0), 0                   | 1 (1.7), 1                    | 0 (0.0), 0            | 1 (0.3), 1           |
| Abdominal pain upper                            | 1 (1.8), 1                  | 0 (0.0), 0                   | 0 (0.0), 0                   | 0 (0.0), 0                   | 0 (0.0), 0                    | 0 (0.0), 0            | 1 (0.3), 1           |
| <b>Nervous system disorders</b>                 |                             |                              |                              |                              |                               |                       |                      |
| All                                             | 0 (0.0), 0                  | 0 (0.0), 0                   | 0 (0.0), 0                   | 2 (3.5), 3                   | 1 (1.7), 1                    | 0 (0.0), 0            | 3 (0.9), 4           |
| Dizziness                                       | 0 (0.0), 0                  | 0 (0.0), 0                   | 0 (0.0), 0                   | 2 (3.5), 2                   | 1 (1.7), 1                    | 0 (0.0), 0            | 3 (0.9), 3           |
| Headache                                        | 0 (0.0), 0                  | 0 (0.0), 0                   | 0 (0.0), 0                   | 1 (1.8), 1                   | 0 (0.0), 0                    | 0 (0.0), 0            | 1 (0.3), 1           |

|                                               | 50 mg<br>E-58425<br>(N=55) | 100 mg<br>E-58425<br>(N=53) | 150 mg<br>E-58425<br>(N=57) | 200 mg<br>E-58425<br>(N=57) | 100 mg<br>Tramadol<br>(N=58) | Placebo<br>(N=54) | Total<br>(N=334) |
|-----------------------------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------------|-------------------|------------------|
| Number of Patients (%), Number of Events      |                            |                             |                             |                             |                              |                   |                  |
| <b>Skin and subcutaneous tissue disorders</b> |                            |                             |                             |                             |                              |                   |                  |
| All                                           | 0 (0.0), 0                 | 0 (0.0), 0                  | 0 (0.0), 0                  | 0 (0.0), 0                  | 1 (1.7), 1                   | 1 (1.9), 1        | 2 (0.6), 2       |
| Drug eruption                                 | 0 (0.0), 0                 | 0 (0.0), 0                  | 0 (0.0), 0                  | 0 (0.0), 0                  | 0 (0.0), 0                   | 1 (1.9), 1        | 1 (0.3), 1       |
| Rash                                          | 0 (0.0), 0                 | 0 (0.0), 0                  | 0 (0.0), 0                  | 0 (0.0), 0                  | 1 (1.7), 1                   | 0 (0.0), 0        | 1 (0.3), 1       |

A subject with more than one finding in a specific category was only counted once.

Percentages based on total no. of subjects in each treatment group

Table is sorted by descending subject count on the PT level

Abbreviations: TEAE – treatment-emergent adverse event

Source: Adapted from Applicant's submission; CSR ESTEVE-SACO4-201; Table 27

### Treatment-Emergent Adverse Events in the Phase 3 Study

In the Phase 3 factorial study (ESTEVE-SUSA-301), the most common TEAEs in all groups were gastrointestinal disorders that were seen more in the tramadol group (87 subjects, 48%), followed by the E-58425 group (63 subjects, 34%), the celecoxib group (46 subjects, 25%), and the placebo group (22 subjects, 25%). The most commonly reported gastrointestinal TEAEs were nausea, vomiting, and constipation. Nervous system disorders were the next most common SOC for TEAEs, with the following PTs having the highest incidence: dizziness (total of 87 subjects, 13.7%), headache (80 subjects, 12.6%), and somnolence (32 subjects, 5%). Most AEs occurred with a similar incidence in the E-58425 group and the tramadol group except somnolence, which occurred higher in the E-58425 group (15 subjects, 8.2%), followed by tramadol (10 subjects, 5.5%), celecoxib group (4 subjects, 2.2%), and placebo (3 subjects, 3.4%) groups. The only other SOC with an incidence of TEAEs in more than 5% of subjects was the Metabolism and Nutrition disorders SOC with an incidence of PT decreased appetite occurring in 6% of subjects in the tramadol group, followed by 3.3% in the E-58425 group, 0.5% in celecoxib, and none in the placebo group. Table 24 shows the summary of AEs in Phase 3 study. Table 25 shows the most frequently reported TEAEs in any treatment group by SOC and PT.

**Table 24: Summary of Adverse Events in Phase 3 Study ESTEVE-SUSA-301**

|                                                | <b>E-58425<br/>(N=183)</b> |               | <b>Tramadol<br/>(N=183)</b> |               | <b>Celecoxib<br/>(N=182)</b> |               | <b>Placebo<br/>(N=89)</b> |               | <b>Total<br/>(N=637)</b> |               |
|------------------------------------------------|----------------------------|---------------|-----------------------------|---------------|------------------------------|---------------|---------------------------|---------------|--------------------------|---------------|
|                                                | <b>n (%)</b>               | <b>Events</b> | <b>n (%)</b>                | <b>Events</b> | <b>n (%)</b>                 | <b>Events</b> | <b>n (%)</b>              | <b>Events</b> | <b>n (%)</b>             | <b>Events</b> |
| All AEs                                        | 131 (71.6)                 | 447           | 136 (74.3)                  | 469           | 115 (63.2)                   | 311           | 61 (68.5)                 | 171           | 443 (69.5)               | 1398          |
| TEAEs                                          | 116 (63.4)                 | 358           | 116 (63.4)                  | 394           | 95 (52.2)                    | 222           | 51 (57.3)                 | 122           | 378 (59.3)               | 1096          |
| Serious TEAEs                                  | 0                          | 0             | 0                           | 0             | 0                            | 0             | 0                         | 0             | 0                        | 0             |
| Drug-related serious TEAEs                     | 0                          | 0             | 0                           | 0             | 0                            | 0             | 0                         | 0             | 0                        | 0             |
| Serious TEAEs leading to death                 | 0                          | 0             | 0                           | 0             | 0                            | 0             | 0                         | 0             | 0                        | 0             |
| TEAEs related to study drug                    | 69 (37.7)                  | 205           | 89 (48.6)                   | 230           | 40 (22.0)                    | 89            | 22 (24.7)                 | 47            | 220 (34.5)               | 571           |
| Severe TEAEs                                   | 2 (1.1)                    | 4             | 4 (2.2)                     | 5             | 2 (1.1)                      | 2             | 2 (2.2)                   | 3             | 10 (1.6)                 | 14            |
| TEAEs requiring additional therapy             | 46 (25.1)                  | 74            | 54 (29.5)                   | 85            | 22 (12.1)                    | 31            | 8 (9.0)                   | 11            | 130 (20.4)               | 201           |
| TEAEs leading to discontinuation of study drug | 3 (1.6)                    | 4             | 3 (1.6)                     | 3             | 0                            | 0             | 0                         | 0             | 6 (0.9)                  | 7             |
| TEAEs of special interest                      | 87 (47.5)                  | 245           | 101 (55.2)                  | 257           | 60 (33.0)                    | 107           | 31 (34.8)                 | 53            | 279 (43.8)               | 662           |

Abbreviations: AE – adverse event; TEAE – treatment-emergent adverse event

Note: The denominator for the percentages is the number of subjects in each treatment group.

<sup>a</sup> Treatment-emergent adverse events were defined as AEs with onset at the time of or following the start of treatment with the study medication, or AEs starting before the start of treatment but increasing in severity or relationship at the time of or after the start of treatment.

Source: Adapted from Applicant's submission; CSR ESTEVE-SUSA-301; Table 12-1 ("Section 14.3, Table 14.3.1.1")

**Table 25: Most Frequently Reported TEAEs in >5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term in Study ESTEVE-SUSA-301**

| <b>System Organ Class Preferred Term</b> | <b>E-58425 (N=183) n (%)</b> | <b>Tramadol (N=183) n (%)</b> | <b>Celecoxib (N=182) n (%)</b> | <b>Placebo (N=89) n (%)</b> | <b>Total (N=637) n (%)</b> |
|------------------------------------------|------------------------------|-------------------------------|--------------------------------|-----------------------------|----------------------------|
| Any adverse event                        | 116 (63.4)                   | 116 (63.4)                    | 95 (52.2)                      | 51 (57.3)                   | 378 (59.3)                 |
| Gastrointestinal disorders               | 63 (34.4)                    | 87 (47.5)                     | 46 (25.3)                      | 22 (24.7)                   | 218 (34.2)                 |
| Nausea                                   | 55 (30.1)                    | 69 (37.7)                     | 30 (16.5)                      | 17 (19.1)                   | 171 (26.8)                 |
| Vomiting                                 | 29 (15.8)                    | 30 (16.4)                     | 4 (2.2)                        | 2 (2.2)                     | 65 (10.2)                  |
| Constipation                             | 4 (2.2)                      | 13 (7.1)                      | 9 (4.9)                        | 3 (3.4)                     | 29 (4.6)                   |
| Nervous system disorders                 | 58 (31.7)                    | 64 (35.0)                     | 40 (22.0)                      | 22 (24.7)                   | 184 (28.9)                 |
| Dizziness                                | 31 (16.9)                    | 34 (18.6)                     | 9 (4.9)                        | 13 (14.6)                   | 87 (13.7)                  |
| Headache                                 | 21 (11.5)                    | 33 (18.0)                     | 20 (11.0)                      | 6 (6.7)                     | 80 (12.6)                  |
| Somnolence                               | 15 (8.2)                     | 10 (5.5)                      | 4 (2.2)                        | 3 (3.4)                     | 32 (5.0)                   |
| Metabolism and nutrition disorders       | 7 (3.8)                      | 11 (6.0)                      | 1 (0.5)                        | 0                           | 19 (3.0)                   |
| Decreased appetite                       | 6 (3.3)                      | 11 (6.0)                      | 1 (0.5)                        | 0                           | 18 (2.8)                   |

Abbreviations: TEAE – treatment-emergent adverse event

Source: Adapted from Applicant's submission; CSR ESTEVE-SUSA-301; Table 12-2 ("Section 14.3, Table 14.3.1.2")

Most of the TEAEs were mild (37.8%) or moderate (19.9%).

Table 26 shows the common TEAEs (>5% of subjects) by severity. Overall, 10 subjects (1.6%) experienced 14 severe TEAEs including 4 subjects (2.2%) in the tramadol group experiencing 5 severe TEAEs (nausea, vomiting, dizziness, headache, and supraventricular tachycardia), followed by 2 subjects (1.1%) in the E-58425 group experiencing 4 severe TEAEs (nausea x2, dizziness, and hot flush), 2 subjects (1.1%) in the celecoxib group experiencing 2 severe TEAEs (headache and pruritus), and 2 subjects (2.2%) in the placebo group experiencing 3 severe TEAEs (pain in extremity, arthralgia, and tendon pain). Nausea was the most common TEAE and had the highest proportion of severe TEAEs with severe nausea occurring in two subjects (1.1%) in the E-58425 group and in one subject (0.5%) in the tramadol group. Severe vomiting was reported in one subject (0.5%) in the tramadol group versus none in the E-58425 group.

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**Table 26: Common TEAEs (>5% of Subjects) in Any Group by Severity, System Organ Class, and Preferred Term in Study ESTEVE-SUSA-301**

| System Organ Class                                   | Preferred Term | Severity | E-58425<br>(N=183)<br>n (%) | Tramadol<br>(N=183)<br>n (%) | Celecoxib<br>(N=182)<br>n (%) | Placebo<br>(N=89)<br>n (%) | Total<br>(N=637)<br>n (%) |
|------------------------------------------------------|----------------|----------|-----------------------------|------------------------------|-------------------------------|----------------------------|---------------------------|
| Any TEAE                                             |                | Mild     | 116 (63.4)                  | 116 (63.4)                   | 95 (52.2)                     | 51 (57.3)                  | 378 (59.3)                |
|                                                      |                | Moderate | 73 (39.9)                   | 64 (35.0)                    | 70 (38.5)                     | 34 (38.2)                  | 241 (37.8)                |
|                                                      |                | Severe   | 41 (22.4)                   | 48 (26.2)                    | 23 (12.6)                     | 15 (16.9)                  | 127 (19.9)                |
|                                                      |                | Severe   | 2 (1.1)                     | 4 (2.2)                      | 2 (1.1)                       | 2 (2.2)                    | 10 (1.6)                  |
| Gastrointestinal disorders                           |                | Mild     | 39 (21.3)                   | 49 (26.8)                    | 33 (18.1)                     | 14 (15.7)                  | 135 (21.2)                |
|                                                      |                | Moderate | 22 (12.0)                   | 36 (19.7)                    | 13 (7.1)                      | 8 (9.0)                    | 79 (12.4)                 |
|                                                      |                | Severe   | 2 (1.1)                     | 2 (1.1)                      | 0                             | 0                          | 4 (0.6)                   |
| Nausea                                               |                | Mild     | 39 (21.3)                   | 48 (26.2)                    | 20 (11.0)                     | 9 (10.1)                   | 116 (18.2)                |
|                                                      |                | Moderate | 14 (7.7)                    | 20 (10.9)                    | 10 (5.5)                      | 8 (9.0)                    | 52 (8.2)                  |
|                                                      |                | Severe   | 2 (1.1)                     | 1 (0.5)                      | 0                             | 0                          | 3 (0.5)                   |
| Vomiting                                             |                | Mild     | 15 (8.2)                    | 13 (7.1)                     | 2 (1.1)                       | 2 (2.2)                    | 32 (5.0)                  |
|                                                      |                | Moderate | 14 (7.7)                    | 16 (8.7)                     | 2 (1.1)                       | 0                          | 32 (5.0)                  |
|                                                      |                | Severe   | 0                           | 1 (0.5)                      | 0                             | 0                          | 1 (0.2)                   |
| Constipation                                         |                | Mild     | 4 (2.2)                     | 10 (5.5)                     | 6 (3.3)                       | 3 (3.4)                    | 23 (3.6)                  |
|                                                      |                | Moderate | 0                           | 3 (1.6)                      | 3 (1.6)                       | 0                          | 6 (0.9)                   |
| Nervous system disorders                             |                | Mild     | 40 (21.9)                   | 50 (27.3)                    | 34 (18.7)                     | 16 (18.0)                  | 140 (22.0)                |
|                                                      |                | Moderate | 17 (9.3)                    | 12 (6.6)                     | 5 (2.7)                       | 6 (6.7)                    | 40 (6.3)                  |
|                                                      |                | Severe   | 1 (0.5)                     | 2 (1.1)                      | 1 (0.5)                       | 0                          | 4 (0.6)                   |
| Dizziness                                            |                | Mild     | 20 (10.9)                   | 29 (15.8)                    | 7 (3.8)                       | 9 (10.1)                   | 65 (10.2)                 |
|                                                      |                | Moderate | 10 (5.5)                    | 4 (2.2)                      | 2 (1.1)                       | 4 (4.5)                    | 20 (3.1)                  |
|                                                      |                | Severe   | 1 (0.5)                     | 1 (0.5)                      | 0                             | 0                          | 2 (0.3)                   |
| Headache                                             |                | Mild     | 16 (8.7)                    | 25 (13.7)                    | 17 (9.3)                      | 4 (4.5)                    | 62 (9.7)                  |
|                                                      |                | Moderate | 5 (2.7)                     | 7 (3.8)                      | 2 (1.1)                       | 2 (2.2)                    | 16 (2.5)                  |
|                                                      |                | Severe   | 0                           | 1 (0.5)                      | 1 (0.5)                       | 0                          | 2 (0.3)                   |
| Somnolence                                           |                | Mild     | 12 (6.6)                    | 9 (4.9)                      | 4 (2.2)                       | 3 (3.4)                    | 28 (4.4)                  |
|                                                      |                | Moderate | 3 (1.6)                     | 1 (0.5)                      | 0                             | 0                          | 4 (0.6)                   |
| General disorders and administration site conditions |                | Mild     | 17 (9.3)                    | 12 (6.6)                     | 15 (8.2)                      | 7 (7.9)                    | 51 (8.0)                  |
|                                                      |                | Moderate | 1 (0.5)                     | 5 (2.7)                      | 1 (0.5)                       | 0                          | 7 (1.1)                   |
| Musculoskeletal and connective tissue disorders      |                | Mild     | 9 (4.9)                     | 9 (4.9)                      | 15 (8.2)                      | 8 (9.0)                    | 41 (6.4)                  |
|                                                      |                | Moderate | 4 (2.2)                     | 3 (1.6)                      | 2 (1.1)                       | 1 (1.1)                    | 10 (1.6)                  |
|                                                      |                | Severe   | 0                           | 0                            | 0                             | 2 (2.2)                    | 2 (0.3)                   |
| Skin and subcutaneous tissue disorders               |                | Mild     | 14 (7.7)                    | 12 (6.6)                     | 7 (3.8)                       | 3 (3.4)                    | 36 (5.7)                  |
|                                                      |                | Moderate | 3 (1.6)                     | 4 (2.2)                      | 1 (0.5)                       | 1 (1.1)                    | 9 (1.4)                   |
|                                                      |                | Severe   | 0                           | 0                            | 1 (0.5)                       | 0                          | 1 (0.2)                   |
| Investigations                                       |                | Mild     | 8 (4.4)                     | 10 (5.5)                     | 10 (5.5)                      | 6 (6.7)                    | 34 (5.3)                  |
|                                                      |                | Moderate | 0                           | 2 (1.1)                      | 3 (1.6)                       | 2 (2.2)                    | 7 (1.1)                   |
| Metabolism and nutrition disorders                   |                | Mild     | 4 (2.2)                     | 11 (6.0)                     | 1 (0.5)                       | 0                          | 16 (2.5)                  |
|                                                      |                | Moderate | 3 (1.6)                     | 0                            | 0                             | 0                          | 3 (0.5)                   |
| Decreased appetite                                   |                | Mild     | 4 (2.2)                     | 11 (6.0)                     | 1 (0.5)                       | 0                          | 16 (2.5)                  |
|                                                      |                | Moderate | 2 (1.1)                     | 0                            | 0                             | 0                          | 2 (0.3)                   |

Abbreviations: TEAE – treatment-emergent adverse event

Each subject will be counted only once within each preferred term. If a subject experiences more than 1 TEAE within a preferred term, only the TEAE with the strongest relationship, as appropriate, was included in the summaries of relationship.

Source: Adapted from Applicant's submission; CSR ESTEVE-SUSA-301; Table 12-3 ("Section 14.3, Table 14.3.1.3").

**Reviewer Comments:**

*The most frequent TEAEs were Gastrointestinal and Nervous system disorders including nausea, vomiting, constipation, dizziness, headache, and somnolence. Reported AEs in all treatment groups are listed in the labels for Ultram and Celebrex. In general, review of TEAEs did not raise any new safety concerns with the proposed product.*

**8.4.6. Laboratory Findings**

Review of laboratory findings including hematology tests, serum chemistry tests, and urinalysis (dipstick) did not show any significant findings of laboratory-related AEs for the analyzed parameters.

**8.4.7. Vital Signs**

During the clinical studies, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) were recorded at screening, prior to administration of study drug, and following administration of study drug or at the end of the study. In Study ESTEVE-SUSA-301, the following abnormal vital signs were reported in the Adverse Events Analysis Dataset: high blood pressure in seven subjects (four in the E-58425 group and three in the placebo group), low blood pressure in five subjects (three in the tramadol group, one in the celecoxib group, and one in the placebo group), tachycardia in two subjects in the tramadol group, and high body temperature (fever or pyrexia) in three subjects (two in the E-58425 group and one in the placebo group). The Applicant's report for Study ESTEVE-SUSA-301 included a lower number of subjects with abnormal vital signs, including two subjects with high blood pressure (one in the E-58425 group and one in placebo group), four subjects with low blood pressure (three in the tramadol group and one in placebo group), and three subjects with pyrexia (two in the E-58425 group and one in the tramadol group). There was no specific trend in the reported abnormal vital signs. In general, review of vital signs did not reveal any specific trend that would suggest a new safety concern in any of the treatment groups.

**8.4.8. Electrocardiograms**

During the clinical studies, an ECG was recorded at screening and after the collection of the last blood sample of the study, or prior to drug administration on Day 1 and before discharge from the study center. Additional ECGs were performed if judged necessary by the physician in charge during the study. Less than 5% of subjects in any treatment group had changes in any ECG parameter from normal at baseline to abnormal during the study. No clinically relevant trend in the measured ECG parameters was observed for any study.

#### 8.4.9. QT

QTc interval was analyzed for a pool of subjects in Study ESTEVE-SACO4-201 (single dose) and Study ESTEVE-SUSA-301 (multiple dose) according to the following categorizations:

- Absolute QTc interval prolongation (msec): QTc interval >450; QTc interval >480; QTc interval >500
- Change from baseline in QTc interval (msec): QTc interval increases from baseline ≥30; QTc interval increases from baseline ≥60

A QTc interval >500 msec was reported in one patient (0.4%) in the E-58425 group compared with zero reports in the tramadol group. A QTc interval increase from baseline to end of study ≥60 msec was reported in one patient (0.4%) in the E-58425 group compared to three (1.3%) patients in the tramadol group, as shown in Table 27. The above-mentioned QTc changes were not reported in any patients in the celecoxib or placebo group.

**Table 27: QTc Categorical Analysis From 12-lead ECGs for Subjects in Study ESTEVE-SACO4-201 and Study ESTEVE-SUSA-301**

| Visit – Timepoint                | E-58425<br>(N=240) |        | Placebo<br>(N=143) |        | Tramadol<br>(N=241) |        | Celecoxib<br>(N=182) |        |
|----------------------------------|--------------------|--------|--------------------|--------|---------------------|--------|----------------------|--------|
|                                  | n                  | (%)    | n                  | (%)    | n                   | (%)    | n                    | (%)    |
| End of study                     |                    |        |                    |        |                     |        |                      |        |
| QTc >450 msec                    | 6/238              | (2.5%) | 2/142              | (1.4%) | 3/239               | (1.3%) | 5/181                | (2.8%) |
| QTc >480 msec                    | 2/238              | (0.8%) | 0/142              | 0      | 0/239               | 0      | 1/181                | (0.6%) |
| QTc >500 msec                    | 1/238              | (0.4%) | 0/142              | 0      | 0/239               | 0      | 0/181                | 0      |
| Increase from screening ≥30 msec | 10/238             | (4.2%) | 2/141              | (1.4%) | 8/239               | (3.3%) | 3/181                | (1.7%) |
| Increase from screening ≥60 msec | 1/238              | (0.4%) | 0/141              | 0      | 3/239               | (1.3%) | 0/181                | 0      |

Abbreviations: ECG – electrocardiogram

Source: Adapted from Applicant's submission; ISS; Table 33

#### Reviewer Comments:

*QT prolongation is linked to  $C_{max}$  value. The labeled doses for the reference products include starting doses for which the  $C_{max}$  value of tramadol and celecoxib components exceed the  $C_{max}$  values of tramadol and celecoxib observed after E-58425 administration in the relative BA studies. Thus, the systemic safety, including QT prolongation, for E-58425 is expected to be comparable to Ultram and Celebrex. The label for Celebrex does not include information about QT changes. The label for Ultram includes the following information under Section 12.2*

#### *Pharmacodynamics:*

*The effect of oral tramadol on the QTcF interval was evaluated in a double-blind, randomized, four-way crossover, placebo-and positive-(moxifloxacin) controlled study in 68 adult male and female healthy subjects. At a 600 mg/day dose (1.5-fold the maximum immediate-release daily dose), the study demonstrated no significant effect on the QTcF interval.*

*The label for Ultram includes the following information under Section 6.2 Postmarketing Experience that is also included in the proposed label for E-58425:*

*QT prolongation/torsade de pointes: Cases of QT prolongation and/or torsade de pointes have been reported with tramadol use. Many of these cases were reported in patients taking another drug labeled for QT prolongation, in patients with a risk factor for QT prolongation (e.g., hypokalemia), or in the overdose setting.*

#### **8.4.10. Immunogenicity**

This section is not applicable.

### **8.5. Analysis of Submission-Specific Safety Issues**

There were no additional safety issues related to E-58425 that warrant further evaluation.

### **8.6. Safety Analyses by Demographic Subgroups**

#### ***Reviewer Comments:***

*Each individual component of E-58425, celecoxib and tramadol, has a relatively well-known safety profile. The relative BA studies performed by the Applicant showed that the  $C_{max}$  value of each component, tramadol and celecoxib, was lower than the respective listed drugs Ultram (or Adolonta) and Celebrex. Safety analysis of E-58425 for demographic subgroups is expected to be comparable to the safety profile of Ultram and Celebrex for demographic subgroups. Thus, the label for E-58425 will include information from the labels for Ultram and Celebrex. The safety findings for demographic subgroups from the clinical studies in this NDA are summarized in this section. In general, review of available data did not raise new safety concerns regarding safety analysis of E-58425 in demographic subgroups.*

#### **Safety Analyses by Age: Pediatric Patients**

The safety and effectiveness of E-58425 in pediatric patients have not been established. The Applicant will perform pediatric studies after approval of their product. Refer to Section 3.2 for details of pediatric studies. Ultram (tramadol) is contraindicated in children younger than 12 years of age, children younger than 18 years of age following tonsillectomy and/or adenoidectomy, and adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to respiratory depression. Given that E-58425 contains tramadol, the same contraindications as for Ultram are proposed for inclusion in E-58425's label.

#### **Safety Analyses by Age: Elderly Patients**

Data for elderly subjects with TEAEs were analyzed in a pool of patients from Study ESTEVE-SACO4-201 (single dose) and Study ESTEVE-SUSA-301 (multiple dose). The Phase 3 study

ESTEVE-SUSA-301 included 58 (9.1%) subjects over 65 years of age. There were no subjects older than 65 years of age in Study ESTEVE-SACO4-201, which is likely related to the study population of patients with pain after molar extraction (the oldest subject in this study was 48 years old). In general, patients over 65 years of age had slightly higher incidence of at least one TEAE compared with younger patients, and a similar trend was noted for the tramadol group and placebo group, as shown in Table 28. There were no notable trends in the available data for SAEs or discontinuation due to AEs in older subjects that would raise new safety concerns.

**Table 28: Summary of TEAEs in Subjects <65 Years of Age and Subjects ≥65 Years of Age in a Pool of Patients From Study ESTEVE-SACO4-201 and Study ESTEVE-SUSA-301**

| Treatment-Emergent Adverse Events            | E-58425 <65 years (N=229) | E-58425 ≥65 years (N=11) | Tramadol <65 years (N=217) | Tramadol ≥65 years (N=24) | Celecoxib <65 years (N=166) | Celecoxib ≥65 years (N=16) | Placebo <65 years (N=136) | Placebo ≥65 years (N=7) |
|----------------------------------------------|---------------------------|--------------------------|----------------------------|---------------------------|-----------------------------|----------------------------|---------------------------|-------------------------|
|                                              | n (%)                     | n (%)                    | n (%)                      | n (%)                     | n (%)                       | n (%)                      | n (%)                     | n (%)                   |
| At least one TEAE                            | 126 (55.0%)               | 7 (63.6%)                | 117 (53.9%)                | 16 (66.7%)                | 89 (53.6%)                  | 6 (13%)                    | 52 (38.2%)                | 4 (57.1%)               |
| At least one Serious TEAE                    | 1 (0.4%)                  | 0                        | 1 (0.5%)                   | 0                         | 0                           | 0                          | 0                         | 0                       |
| At least one Severe TEAE                     | 2 (0.9%)                  | 0                        | 4 (1.8%)                   | 1 (4.2%)                  | 2 (1.2%)                    | 0                          | 2 (1.5%)                  | 0                       |
| At least one TEAE Leading to Discontinuation | 3 (1.3%)                  | 0                        | 2 (0.9%)                   | 1 (4.2%)                  | 0                           | 0                          | 0                         | 0                       |

Abbreviations: TEAE – treatment-emergent adverse event  
Source: Reviewer-generated, based on ISS, tables 34 and 35

### Safety Analyses by Race

No significant difference in safety was noted in subgroups by race.

### Safety Analyses by Sex

No significant difference in safety was noted by sex.

## 8.7. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted in the development program.

## **8.8. Additional Safety Explorations**

### **8.8.1. Human Carcinogenicity or Tumor Development**

There are no animal or laboratory studies with E-58425 to evaluate carcinogenicity or tumor development. Available data for each individual component of the drug, celecoxib and tramadol, will be included in the label.

### **8.8.2. Human Reproduction and Pregnancy**

There are no data for use of E-58425 in pregnant women. In an animal reproduction study, oral administration of E-58425 to pregnant rabbits during the period of organogenesis resulted in embryo-fetal deaths and teratogenicity, based on a marginal increase of incidence of vertebral defects. Refer to the nonclinical review in Document Archiving, Reporting and Regulatory Tracking System (DARRTS) for further details.

### **8.8.3. Pediatrics and Assessment of Effects on Growth**

The effect of E-58425, if any, on the later growth, development, and functional maturation of the child is unknown. Refer to Section 3.2 for details of required pediatric studies.

### **8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

E-58425 contains tramadol. All approved tramadol-containing products are currently Schedule IV controlled substances under the Controlled Substances Act. Tramadol is an opioid and is considered a substance with a high potential for abuse, misuse, addiction, and criminal diversion. Refer to the review by the Controlled Substance Staff for further details.

## **8.9. Safety in the Postmarket Setting**

### **8.9.1. Safety Concerns Identified Through Postmarket Experience**

E-58425 has not been marketed anywhere in the world. Celecoxib and tramadol have been widely marketed worldwide for more than 20 years and have well-known safety profiles. The safety of celecoxib and tramadol have been under regular review through pharmacovigilance.

Recent pharmacovigilance, epidemiology, and drug utilization reviews have been completed to examine recent data for marketed tramadol-containing products.

The Division of Pharmacovigilance II recently completed a pharmacovigilance review to assess for new safety concerns relating to tramadol. The review included an aggregate analysis of AEs reported to the FDA Adverse Event Reporting System for tramadol, tramadol-specific AEs

reported in the published literature (PubMed), and analysis of FDA Adverse Event Reporting System data in Empirica Signal, one of FDA's primary data mining tools. This analysis resulted in the identification of four potential signals that we determined to be of significant clinical importance. These events are hypoglycemia, hyponatremia, hallucinations, and mania. The Division of Pharmacovigilance II is currently completing comprehensive, individual reviews for each of these potential signals with a possible outcome of updating the prescribing information, if needed.

The Office of Epidemiology and the Drug Utilization Team performed a postmarket review of concomitant use of tramadol and celecoxib and did not find new safety concerns. Refer to the review from Drug Utilization Team/Office of Surveillance and Epidemiology for details.

In conclusion, no additional safety issues identified through U.S. and foreign postmarket experience are recommended for inclusion in labeling at the time of this review.

### **8.9.2. Expectations on Safety in the Postmarket Setting**

E-58425 contains tramadol, which is an opioid. Thus, E-58425 has all the risks associated with opioid medications, including abuse, misuse, addiction, and criminal diversion.

There are no specific characteristics of E-58425 that would be expected to increase or decrease the risk of misuse, abuse, opioid use disorder, and related adverse outcomes such as overdose and infectious complications of injection compared with other opioids. However, given that E-58425 is a co-crystal containing an opioid product, the risks of unintended use of E-58425 should be evaluated. Although a co-crystal is not a new single API and is treated as a fixed-dose combination, potential risks associated with unintended use of E-58425, as a co-crystal containing tramadol should be further evaluated to inform whether co-crystal formulation of tramadol would expose public to any additional risks that would outweigh the analgesic benefits of E-58425.

If approved, celecoxib and tramadol oral tablets (NDA 213426), will be required to become a member of the Opioid Analgesic REMS to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS is a shared system REMS that was initially approved as the Extended-Release (ER) and Long-Acting (LA) (ER/LA) REMS in July 2012 and was expanded in September 2018 to include all application holders of IR opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program. Refer to the Division of Risk Management summary for further details.

### **8.9.3. Additional Safety Issues From Other Disciplines**

Given that E-58425 is a co-crystal containing an opioid product, the potential risks of

unintended use of E-58425 should be further evaluated. Although a co-crystal is not a new single API and is treated as a fixed-dose combination, E-58425 contains an opioid product and requires additional evaluation to inform its benefit-risk profile in the context of broader public health. Additionally, if E-58425 is misused via unintended routes, there may be risks due to the celecoxib component of E-58425. On February 13, 2020, the Division requested that the Applicant perform further assessment of potential risks of E-58425 via unintended routes of administration to assess whether the co-crystal formulation of celecoxib and tramadol would expose the public to any additional risks. On March 02, 2020, the Applicant provided a toxicological risk assessment for intravenous injection of E-58425 to inform the benefit-risk profile of E-58425. This amendment is under review by nonclinical team at the time of this review.

### **8.10. Integrated Assessment of Safety**

E-58425 contains celecoxib and tramadol, which are analgesic products with different mechanisms of action. Celecoxib is an NSAID with selective COX-2 inhibition activity. Tramadol is a  $\mu$ -receptor agonist and a serotonin–norepinephrine reuptake inhibitor. Celecoxib and tramadol have been marketed for more than 20 years with relatively well-characterized safety profiles. Postmarket safety data related to concomitant use of celecoxib and tramadol did not raise any new safety concerns.

Relative BA studies of E-58425 in single-dose studies (ESTEVE-SACO4-104, ESTEVE-SACO4-102, ESTEVE-SACO4-103, and ESTEVE-SUSA-101) and a multiple-dose study (ESTEVE-SACO4-105) demonstrated that the  $C_{max}$  of each product (celecoxib and tramadol) is comparable or lower than the individual listed drugs, Celebrex and Ultram, respectively. In the factorial study ESTEVE-SUSA-301, tramadol was used 50 mg every 6 hours, which is consistent with the labeling for Ultram for managing acute pain. The dose of tramadol (Ultram or Adolonta) in the relative BA studies was 100 mg as single dose or 100 mg every 12 hours as multiple dose. The Ultram 100 mg dose is within the recommended starting dose range described in the Ultram label. Given the comparable or lower systemic exposure to each product, celecoxib and tramadol, the systemic safety of the combination product, E-58425, is expected to be comparable to the systemic safety of each individual product.

In the clinical studies performed by the Applicant, the most common AEs reported with E-58425 were comparable to those reported with tramadol, including nausea and vomiting in SOC Gastrointestinal disorders and somnolence and dizziness in Nervous system disorders. Per Ultram's label, the most common TEAEs with Ultram are dizziness/vertigo, nausea, constipation, headache, somnolence, vomiting, and pruritus. Per Celebrex's label, its most common adverse drug reactions are abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, and rash. No unexpected safety issues were reported with the use of E-58425 in

clinical studies performed by the Applicant. Review of SAEs in studies performed by MRL did not raise any new safety concerns.

The proposed dosing regimen for E-58425 is 200 mg every 12 hours, which contains celecoxib 112 mg and tramadol 88 mg every 12 hours, and a total dose of celecoxib 224 mg and tramadol 176 mg per day. The maximum recommended dose for both celecoxib and tramadol is 400 mg per day. The amount of celecoxib and tramadol in E-58425 does not exceed the recommended doses of the individual components per the labels for Celebrex and Ultram, respectively. However, the recommended labeled dosage for the starting dose of Ultram is lower than the proposed dosing regimen for E-58425. The label for Ultram states the following:

For patients not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: Start ULTRAM at 25 mg/day and titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to AEs associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

The dosing regimen for E-58425 contains a higher amount of tramadol (88 mg per dose and 176 mg per day) compared to the recommended starting regimen for Ultram in its label (25 mg per day). In the controlled clinical trials performed by the Applicant, tramadol was dosed 50 mg every 6 hours. The TEAEs in the E-58425 group were comparable to those in the tramadol group. Additionally, in the clinical setting tramadol may be prescribed as 50 to 100 mg every 6 hours. Furthermore, the recommended dosing regimen for Ultracet (tramadol hydrochloride 37.5 mg and acetaminophen 325 mg) is two tablets every 4 to 6 hours, which contains tramadol 75 mg every 4 to 6 hours. The label for Ultracet states the following:

Initiate treatment with two tablets every 4 to 6 hours as needed for pain relief; maximum of 8 tablets per day.

Therefore, the proposed dosing regimen for E-58425 contains comparable amount of tramadol to other approved tramadol products.

E-58425 is a fixed-dose combination product dosed every 12 hours, which provides less flexibility in making dose adjustments. This may be relevant in situations where patients do not

tolerate the recommended initial dose of tramadol, which is on the upper end of the recommended dose range in the Ultram label.

The main safety issue related to E-58425 is related to the potential risks associated with unintended use of the product as a co-crystal containing an opioid. There are no specific characteristics of E-58425 that would be expected to increase or decrease the risk of misuse, abuse, opioid use disorder, and related adverse outcomes such as overdose and infectious complications of injection compared to other opioids. However, given that E-58425 is a co-crystal containing an opioid product, the potential risks of unintended use of E-58425 should be further evaluated to inform the benefit-risk profile of the product in the context of broader public health, which is under review by nonclinical team at the time of this review.

Approved tramadol products are classified under Schedule IV of the Controlled Substances Act by the United States Drug Enforcement Administration. Tramadol is an opioid and is considered a substance with a high potential for abuse, misuse, addiction, and criminal diversion. If approved, E-58425 will be subject to the Opioid Analgesic REMS to ensure that the benefits of E-58425 outweigh potential risks in the outpatient setting. Refer to the review by the Controlled Substance Staff for further details.

## 9. Advisory Committee Meeting and Other External Consultations

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Section 106 of the Comprehensive Addiction and Recovery Act of 2016 requires FDA to refer NDAs for opioids to an advisory committee before approval, unless such a referral is not in the interest of protecting and promoting public health and it is not necessary based on a review of the relevant scientific information (Congress 2016). The NDA 213426 for celecoxib and tramadol, tablet, was discussed at a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on January 15, 2020. The following is a brief summary of the two discussion topics and one voting question during the meeting. See the full transcript of the meeting for details, when available.

**Discussion Topic #1:** Considering the abuse potential of E-58425 and its proposed use for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate, please discuss any concerns you have regarding the impact of this product, if approved, on public health.

**Committee Discussion:** *In considering the abuse potential of tramadol 44 mg and celecoxib 56mg tablets and its proposed use, some Committee members had concerns regarding the impact of this product on public health (if approved), and expressed the need for comparison data of the combination product to its individual ingredients when taken together as tramadol*

*plus celecoxib, and to celecoxib alone at a higher therapeutic dose. These Committee members added that the efficacy of this combination product for 12 hours could be due to the effects of celecoxib, and thus there would be no benefit of introducing another opioid option in terms of public health. Other Committee members noted the lack of flexibility for titration in a fixed-dose combination product, lack of data on the risks of intravenous abuse of the co-crystal formulation, concerns about the toxicity of celecoxib if abused by the intravenous route, and the financial considerations of the combination product compared with the currently approved generic options of each ingredient. Those Committee members who did not express concerns regarding the public health impact stated that both individual ingredients have already been shown to have favorable profiles, and therefore agreed that this combination product of tramadol 44 mg and celecoxib 56 mg tablets could be a better alternative to what is currently available to treat acute pain in terms of public health. Other Committee members agreed and used the term “tramadol light” for the benefits of tramadol observed in the relatively low-dose of tramadol in the combination product compared with other available tramadol products while having demonstrated efficacy and, thus, the possibility of less abuse in terms of public health.*

**Discussion Topic #2:** Discuss whether the benefits outweigh the risks for the proposed indication. Discuss any additional data that are needed for this application to be approved.

**Committee Discussion:** *Several Committee members who agreed that the benefits of tramadol 44 mg and celecoxib 56 mg tablets outweighed the risks for the proposed indication expressed that tramadol and celecoxib have been individually available for a long time, and therefore combining the two ingredients as a lower-dose combination product would make an alternative available to opioid treatment currently used for acute pain. These Committee members also noted that this combination product may decrease the use of opioid rescue medications and the number of pills that are needed for pain management.*

*The Committee members who disagreed that the benefits outweighed the risks for the proposed indication argued that the combination product is not effective, and patients will need some type of rescue pain medication, thus increasing the potential of adding on another, stronger opioid. Other Committee members added that combination tablets decrease flexibility in titrating doses. These Committee members were concerned about the potential issues involved in using the combination tablet once pain is less severe and an opioid is no longer needed.*

**Advisory Committee Vote:** Do you recommend approval of the proposed dose of tramadol 44 mg and celecoxib 56 mg tablets for the proposed indication of the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate?

**Vote Result:** Yes: 13 No: 13 Abstain: 0

**Committee Discussion:** *The Committee members were split on whether they recommend approval of tramadol 44 mg and celecoxib 56 mg tablets for the proposed indication. The majority of those who voted “Yes” indicated that the overall benefits outweighed the risks for the proposed indication. These committee members believed that efficacy was demonstrated in the Phase 3 study and that the pharmacokinetic data suggested an efficacy and safety advantage over tramadol and celecoxib when used individually. Other Committee members who were in favor of approval noted a potential advantage of the combination product, i.e., because tramadol is a Schedule IV controlled substance the product carries less risk compared with other short-acting Schedule II opioids and may provide an alternative to use of short-acting Schedule II opioids for post-operative pain management, which could have a positive public health impact.*

*The Committee members who voted “No” stated that the benefit-risk profile was not favorable and noted the lack of comparative data of the combination product to doses of its single ingredients, tramadol and celecoxib, when used together. Some of these Committee members voiced concerns that the perception of tramadol 44 mg and celecoxib 56 mg tablets being safer may lead to over-prescribing, abuse/misuse, and potential for downstream effects. The committee members who voted “No” were concerned that there were no data available on potential risks of use of E-58425 via untended routes, injection of a co-crystal product, or injection of the celecoxib component of the product.*

Given the concern about the risks of intravenous abuse of the product and the impact of this issue on public health, the Division sent an information request to the Applicant requesting a risk assessment for E-58425 that addresses the potential toxicities related to both the active and inactive ingredients should it be administered into the intravascular space.

## 10. Labeling Recommendations

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### 10.1. Prescription Drug Labeling

The labeling review is ongoing at the time of this review. The Applicant submitted the most current version of the Prescribing Information on October 31, 2019 in response to the Division’s request to clarify the clinical and nonclinical information to support the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of the labeling.

At the time of this review, the Division of Medication Error Prevention and Analysis and the Office of Medication Error Prevention and Risk Management have not agreed with the proposed proprietary name for the product.

The Applicant has proposed labeling that relies on the information available for the two RLDs, Ultram (Tramadol) and Celebrex (Celecoxib). Given that E-58425 is a combination product containing celecoxib and tramadol, the label for E-58425 is being reviewed to ensure that relevant information from both RLDs is included in the label. Additionally, the relevant information from the opioid class labeling template and the NSAID class labeling template will be reflected in the label for E-58425.

The following changes were made to the Applicant's proposed PI from a clinical perspective:

- In BOXED WARNING, the Applicant listed all warnings for tramadol first, followed by cardiovascular and gastrointestinal warnings for celecoxib. Warnings should be listed in decreasing order of clinical importance. Therefore, cardiovascular and gastrointestinal warnings for celecoxib were moved up.
- Section (b) (4) Safe Reduction or Discontinuation was updated to reflect the most recent class labeling change for opioids.
- Section (b) (4) Cardiovascular Thrombotic Events was edited to include relevant information from the NSAID class labeling template.
- Section (b) (4) Heart Failure and Edema was edited to include relevant information from the NSAID class labeling template.
- Section 6.1
  - Clinical Trials Experience should be updated to reflect correct number of subjects who were exposed to study drug.
  - Table 1 in Section 6.1 should be updated to reflect adverse reactions appropriately.
  - Information (b) (4) was deleted.
- Section 9.3 Dependence was updated to reflect recent opioid class labeling changes.
- Section 14 Clinical Studies was edited.

## 10.2. Nonprescription Drug Labeling

Not applicable.

## 11. Risk Evaluation and Mitigation Strategies

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If approved, celecoxib and tramadol oral tablets (NDA 213426) will be required to become a member of the Opioid Analgesic REMS to ensure that the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS is a shared system REMS that was initially approved as the ER/LA REMS in July 2012 and was expanded in September 2018 to include all application holders of IR opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program.

Clinical Review  
NDA 213426  
E-58425 [TRADENAME] (celecoxib and tramadol, tablet)

Refer to the Division of Risk Management summary for further details.

## **12. Postmarketing Requirements and Commitments**

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A toxicology study in juvenile animals and a pharmacokinetic, efficacy, and safety study in pediatric patients 12 to <17 years of age will be required under the Pediatric Research Equity Act.

## 13. Appendices

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### 13.1. References

Chai, G, J Xu, J Osterhout, MA Liberatore, KL Miller, C Wolff, M Cruz, P Lurie, and G Dal Pan, 2018, New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015, *Anesthesiology*, 128(5):953-966.

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Ratitch, B and M O'Kelly, 2011, Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures, PharmaSUG, accessed February 11, 2020, <http://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf>.

The European Agency for the Evaluation of Medicinal Products, May 2003, Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain, accessed December 5, 2019, [https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-clinical-investigation-medicinal-products-treatment-nociceptive-pain\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/note-guidance-clinical-investigation-medicinal-products-treatment-nociceptive-pain_en.pdf).

## 13.2. Financial Disclosure

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Some details of the form were not clear in the initial submission including the total number of investigators. An information request was sent, and the Applicant provided updated information. Details of the financial disclosure are outlined below.

### Covered Clinical Study: ESTEVE-SUSA-301

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| Was a list of clinical investigators provided?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant)        |
| Total number of investigators identified: <u>120</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                         |                                                                  |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                                  |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                         |                                                                  |
| <p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in Sponsor of covered study: _____</p> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request details from Applicant)     |
| Is a description of the steps taken to minimize potential bias provided?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                         |                                                                  |
| Is an attachment provided with the reason?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Yes <input type="checkbox"/>            | No <input type="checkbox"/> (Request explanation from Applicant) |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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SEPIDEH HAGHPANAH  
03/16/2020 10:44:22 AM

PAMELA J HORN  
03/16/2020 11:13:39 AM

YAN ZHOU  
03/16/2020 11:58:56 AM

JINGLIN ZHONG  
03/16/2020 01:02:59 PM

LEI NIE  
03/16/2020 01:04:47 PM