2 SYNOPSIS

Sponsor:
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Individual Study Table Referring to Part of the Dossier

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Name of Finished Product:
Tramadol/diclofenac FDC

Volume:

Name of Active Ingredient:
Tramadol hydrochloride/
diclofenac sodium

Page:

Study Title:
A randomized, double-blind, multi-site, comparator-controlled, Phase III trial to evaluate the efficacy and safety of a fixed-dose combination of tramadol hydrochloride and diclofenac sodium in acute moderate to severe pain after third molar extraction

Investigators and Study Sites: Coordinating Investigator [redacted] DMD, PhD; Multi-site (8 sites in Mexico)

Publication (reference): None

Studied Period:
26 August 2017 (first patient enrolled) to 22 March 2018 (last patient completed)

Phase of Development: Phase III

Objectives: The overall objective of the trial was to evaluate the analgesic efficacy and safety of the tramadol HCl/diclofenac sodium fixed-dose combination (FDC) at 2 dose levels (50 mg/50 mg, 25 mg/25 mg) in comparison to the monotherapy of diclofenac sodium 50 mg and tramadol HCl 50 mg.

The primary objective was to demonstrate the analgesic efficacy of the tramadol HCl/diclofenac sodium FDC at 2 dose levels (50 mg/50 mg, 25 mg/25 mg) in comparison to the monotherapy of diclofenac sodium 50 mg and tramadol HCl 50 mg.

The specific primary objective was to demonstrate that:

- Either tramadol HCl/diclofenac sodium 50 mg/50 mg has superior analgesic efficacy than monotherapy with diclofenac sodium 50 mg,
- Or tramadol HCl/diclofenac sodium 50 mg/50 mg has superior analgesic efficacy than monotherapy with tramadol HCl 50 mg,
- Or tramadol HCl/diclofenac sodium 25 mg/25 mg is not inferior to monotherapy with tramadol HCl 50 mg,
- Or tramadol HCl/diclofenac sodium 25 mg/25 mg is not inferior to monotherapy with diclofenac sodium 50 mg

The secondary objectives of the trial included the following:

- To further explore the efficacy of the tramadol HCl/diclofenac sodium FDC at 2 dose levels (50 mg/50 mg, 25 mg/25 mg) in comparison to the monotherapy of diclofenac sodium 50 mg and tramadol HCl 50 mg.
- To compare the overall impression of the subject on the treatment they received.
- To evaluate the safety profile of the FDC product in comparison to the safety profiles of the monotherapies.

Methodology: This was a prospective, randomized, double-blind, diclofenac- and tramadol-controlled, parallel-group, multi-site, interventional Phase III trial to evaluate the analgesic efficacy and safety of tramadol HCl/diclofenac sodium (25 mg/25 mg, 50 mg/50 mg) FDC in comparison to tramadol HCl (50 mg) and/or diclofenac sodium (50 mg) alone in subjects with moderate to severe pain after third molar extraction at 8 sites in Mexico. Eligible subjects were scheduled to receive 3 doses of blinded investigational medicinal product (IMP) over a 24-hour period.

The trial included 4 visits. Visit 1 was the enrollment visit (Days -10 to -1) during which informed consent was obtained and initial subject eligibility was determined. Subjects subsequently underwent ≥ 24-hour washout of previously used analgesics prior to Visit 2. At Visit 2 (Day 1), subject eligibility was confirmed and the third molar extraction procedure was performed following standardized local anesthesia and surgical procedures. Subjects with a pain intensity score ≥ 5 on an 11-point numerical rating scale (NRS; 0 to 10) within 4 hours after surgery were allocated (randomized) to treatment, with pain intensity at baseline (moderate: 5 to 6; severe: 7 to 10) as a stratification factor. The first dose of IMP was administered at the trial site when the postsurgical

pain intensity reached ≥ 5 on the NRS. Rescue medication comprising ibuprofen 400 mg orally (first-line therapy) and ketorolac tromethamine 30 mg intramuscularly (second-line therapy) for insufficient pain relief was allowed, however subjects were encouraged to wait at least 120 minutes after the first dose of IMP before taking any rescue medication. Cold compresses or ice bags on cheeks were allowed 4 hours after IMP administration, but not within 30 minutes before pain assessments. The second dose of IMP was administered at the trial site 8 hours (± 10 minutes) after the first dose, after which subjects could be discharged. The third dose of IMP was taken in the outpatient setting 16 hours (± 1 hour) after the first dose was administered. Visit 3 (Day 2) was the end-of-treatment visit and occurred approximately 24 hours after the first dose of IMP. Visit 4 (Day 14) was the follow-up safety (adverse event) assessment, and was conducted either via phone or in person at the trial site.

Efficacy measurements are summarized in the following table and were recorded in an in-clinic and in-home patient diary.

Efficacy Measurement	Brief Description
Pain Intensity [a]	Measured using an 11-point NRS by answering the following question: "*Please rate your pain by selecting the one number that best describes how much pain you have right now.*" Scores ranged from 0 (no pain) to 10 (pain as bad as you can imagine, and were categorized as None (0), Mild (≥ 1 and < 5), Moderate (≥ 5 and ≤ 6), and Severe (≥ 7). Baseline was the score assessed before the first dose of IMP, and was used for stratification.
Pain Relief [b]	Measured as compared to baseline using a 5-point VRS by completing the following statement: "*My relief from starting pain is*" Scores ranged from 0 (none) to 4 (complete).
TOTPAR	Derived from the 5-point VRS, and calculated at 4, 6, and 8 hours as defined in Criteria for Evaluation.
Time to Onset of Pain Relief	Two stopwatches were started by the investigator when the first dose of IMP was administered. The subject stopped stopwatch 1 at the time of first perceptible pain relief, and stopped stopwatch 2 at the time of meaningful pain relief.
Time to Achieve a 50% Reduction of Baseline Pain [c]	Assessed by answering the following statement with YES or NO: "*My starting pain is at least half gone.*" Each assessment was independent of previous assessments.
Rescue Medication Request and Intake	The day/actual time of rescue medication request and dose of rescue medication administered was documented. The time from baseline to the first dose of rescue medication and the amount of rescue medication used within 24 hours after surgery were calculated.
Subject's Global Evaluation of Treatment (5-point Likert Scale) [d]	Assessed by answering the following question: "*How would you rate the study medication you received for pain?*" Ratings ranged from Poor (0) to Excellent (4).

IMP = investigational medicinal product; NRS = numeric rating scale; TOTPAR = total pain relief; VRS = verbal rating scale

[a] Conducted before the first dose of IMP, and 15, 30, 45, 60, and 90 minutes (± 2 minutes), and 2, 3, 4, 5, 6, 7, 8, 16 and 24 hours (± 6 minutes) after the first dose of IMP. Recorded in an in-clinic and in-home patient diary.

[b] Conducted 15, 30, 45, 60, and 90 minutes (± 2 minutes), and 2, 3, 4, 5, 6, 7, 8, and 16 hours (± 6 minutes) after the first dose of IMP. Recorded in an in-clinic and in-home patient diary.

[c] Conducted 15, 30, 45, 60, and 90 minutes (± 2 minutes), and 2, 3, 4, 5, 6, 7, 8, and 24 hours (± 6 minutes) after the first dose of IMP.

[d] Performed 8 hours after the first dose of the IMP or immediately before the first dose of rescue medication (whichever was first), and 24 hours after the first dose of IMP.

Safety was assessed throughout the trial (Visit 1 to Visit 4), primarily through assessment of all reported or observed adverse events (AEs). Clinical laboratory assessments and vital sign measurements were also collected to determine subject eligibility. Posttreatment clinical laboratory and vital sign assessments were not performed.

Number of Patients (Planned and Analyzed):
Planned: enroll 1065 subjects (ie, signed informed consent), allocate 800 subjects to treatment (200 per treatment arm), stratified by pain intensity at baseline

Actual: enrolled (signed informed consent) 1151 subjects, allocated 829 subjects (208 to diclofenac sodium 50 mg, 206 to tramadol HCl 50 mg, 206 to tramadol HCl/diclofenac sodium 25 mg/25 mg, 209 to tramadol HCl/diclofenac sodium 50 mg/50 mg)

Analyzed: 825 subjects were analyzed for efficacy; 826 subjects were analyzed for safety

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were >18 to 60 years of age, required extraction of ≥ 3 third molars with 2 mandibular impacted third molars, and were in good general health. Subjects were excluded if they had a hypersensitivity to the IMPs, the anesthetic used during surgery, or the rescue medication (ibuprofen, ketorolac); known alcohol or drug abuse in the last 6 months; any history of seizures; molars linked to the mandibular canal; received any analgesic medication other than short-acting pre-operative or intraoperative anesthetic agents within 24 hours before taking IMPs; received >300 mg of lidocaine in total; or received an analgesic medication other than the IMPs immediately after the surgical procedure, baseline pain intensity after oral surgical procedure remained <5 points on the 11-point NRS.

Test Product, Dose and Mode of Administration, Batch Number:

Tramadol HCl/diclofenac sodium 25 mg/25 mg FDC immediate-release tablets for oral administration (batch number: 1701031);

Tramadol HCl/diclofenac sodium 50 mg/50 mg FDC immediate-release tablets for oral administration (batch number: 1703011)

Duration of Treatment: 3 doses administered every 8 hours (Q8H) over 24 hours

Reference Therapy, Dose and Mode of Administration, Batch Number:

Diclofenac sodium 50 mg enteric-coated tablets for oral administration (batch number: K0486);

Tramadol HCl 50 mg immediate-release capsules for oral administration (batch number: 1701011);

Matching placebo for diclofenac, tramadol and tramadol HCl/diclofenac sodium 50/50 (batch number: PL170401), and matching placebo for tramadol HCl/diclofenac sodium 25/25 (batch number: PL170402)

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint: Total pain relief after 4 hours (TOTPAR4), calculated as a weighted sum of the observed pain relief scores during the first 4 hours after the first dose with weights proportional to the time since the last pain relief assessment. Total pain relief (TOTPAR) was defined as ΣPRt x (time [hours] elapsed since previous observation) where PRt is the Pain Relief at time point t (based on VRS) in comparison to the assessment before administration of IMPs. The subject's pain relief is assessed using a 5-point VRS.

Secondary Efficacy Endpoints: TOTPAR6 and TOTPAR8 post-dose; SPID at 4, 6, 8, and 24 hours post-dose; time to achieve a 50% reduction in baseline pain (pain at least half gone); time to onset of first perceptible pain relief (stopwatch 1); time to onset of meaningful pain relief (stopwatch 2); time to intake of first rescue medication dose; and subject's global evaluation of the treatment (5-point Likert Scale) 8 hours after the first dose of IMPs or before first intake of rescue medication (whichever was first) and 24 hours after the first dose of IMP. SPID was defined as ΣPIDt x (time [hours] elapsed since previous observation) where PIDt is defined as the difference between baseline pain intensity and pain intensity at time point t (eg, baseline score – time point t score), where pain intensity is evaluated using an 11-point NRS.

Exploratory Efficacy Endpoints: Pain relief score after first dose over time; pain intensity score after the first dose over time (based on NRS); pain intensity differences (PID) after the first dose over time; peak pain relief score; peak PID score; time to request first dose of rescue medication; time to peak pain relief score; and time to peak PID score.

Safety:

The safety endpoints of the study were the incidence and type of adverse events. Safety and tolerability was assessed throughout the study by monitoring and evaluating treatment-emergent adverse events (TEAEs), including any complications resulting from IMP administration. Vital signs and clinical laboratory parameters were also assessed prior to treatment allocation.

Statistical Methods:

Efficacy:

The following data sets were used in the analysis of efficacy:

- Full Analysis Set (FAS) – comprised of all subjects who were allocated and treated, and with at least 1 non-missing pain relief assessment during the first 4 hours post-baseline. Analyses on the FAS were conducted according to allocated treatment.
- Per Protocol Set (PPS) – comprised a subset of subjects in the FAS without any major protocol deviations affecting the primary endpoint analysis. Only subjects with no rescue medication use in the first 120 minutes after the first dose, who completed at least a follow-up of 4 hours, and who complied with the protocol procedures were included in the PPS. Analyses on the PPS were conducted according to actual treatment received.

Primary Endpoint Analysis: The primary efficacy analysis of the primary efficacy endpoint (TOTPAR4) was performed on the FAS, and repeated as sensitivity analysis on the PPS. The primary objective was investigated by 4 formal statistical tests (see below). To control the family-wise type I error rate at the prespecified 1-sided significance level of $\alpha = 2.5\%$, a Bonferroni-Holm procedure was used.

Test	Description	Null Hypothesis	Alternative Hypothesis
T1	Superiority of tramadol HCl/diclofenac sodium 50 mg/50 mg vs tramadol HCl 50 mg	$H_{(01)}$: $\mu_{T50} - \mu_{ADL50/50} \geq 0$	H_{A1}: $\mu_{T50} - \mu_{ADL50/50} < 0$
T2	Superiority of tramadol HCl/diclofenac sodium 50 mg/50 mg vs diclofenac sodium 50 mg	$H_{(02)}$: $\mu_{D50} - \mu_{ADL50/50} \geq 0$	H_{A2}: $\mu_{D50} - \mu_{ADL50/50} < 0$
T3	Noninferiority of tramadol HCl/diclofenac sodium 25 mg/25 mg vs tramadol HCl 50 mg	$H_{(03)}$: $\mu_{T50} - \mu_{ADL25/25} \geq \Delta$	H_{A3}: $\mu_{T50} - \mu_{ADL25/25} < \Delta$
T4	Noninferiority of tramadol HCl/diclofenac sodium 25 mg/25 mg vs diclofenac sodium 50 mg	$H_{(04)}$: $\mu_{D50} - \mu_{ADL25/25} \geq \Delta$	H_{A4}: $\mu_{D50} - \mu_{ADL25/25} < \Delta$

$\Delta = 1.5$ was the noninferiority margin; ADL = Adorlan (tramadol HCl/diclofenac sodium); D = diclofenac sodium; T = tramadol hydrochloride

The trial was considered positive if at least 1 of the 4 statistical tests rejected the corresponding null hypothesis. The primary analysis used an analysis of covariance (ANCOVA) model with treatment, site, and baseline pain (measured on an 11-point NRS) as covariates. The pain intensity score assessed before IMP intake was considered the baseline pain intensity.

Missing pain relief assessments in the first 4 hours after first dose as well as pain relief assessments after start of intake of rescue medication were imputed using the last observation carried forward (LOCF) with delta substitution method.

For sensitivity analyses on the FAS, missing and disregarded pain relief assessments were imputed by various methods listed below. After imputation of the missing data, the same analysis described for the primary endpoint was performed.

- LOCF Only
- LOCF with zero substitution: LOCF for intermittent missing data and substitution by zero (no relief from baseline pain) for missing data after premature discontinuation from the trial or disregarded pain relief assessments after the start of rescue medication.
- Worst observation carried forward (WOCF) with LOCF: WOCF for missing pain assessment due to rescue medication, and LOCF for all other missing pain assessments.
- WOCF only

Secondary Efficacy Analyses: TOTPAR6, TOTPAR8, and SPID were analyzed with the same ANCOVA model as the primary analysis. Subject's global evaluation of treatment were descriptively summarized. Secondary endpoints related to time to onset were presented using Kaplan-Meier plots. Medians were compared across the arms using Wilcoxon log-rank test, and hazard ratios (HRs) were compared across the arms using Cox Hazard Ratio model. Time to onset was defined as the elapsed time from the administration of IMP to the time when the subject reported the event (50% reduction of baseline pain, perceptible pain relief, meaningful pain relief, and request/intake of rescue medication, peak pain intensity, and peak pain relief – each separately). As indicated above, times to onset of first perceptible relief and time to meaningful relief were recorded from 2 stopwatches actuated by the subject. Subjects without perceptible or meaningful pain relief were censored at the end of the 8-hour period or first use of rescue medication (whichever was first).

Exploratory Efficacy Analyses: Pain relief score over time, pain intensity score over time, PID over time, peak

pain relief score, and peak PID score were analyzed with the same ANCOVA model as the primary analysis. Endpoints related to time to onset were presented with the same analysis as secondary endpoints related to time.

Subgroup Analyses:

Subgroup analyses were performed for the primary efficacy variable with subjects categorized as having moderate pain intensity (NRS score: 5 or 6) at baseline and as having severe pain intensity (NRS score: 7 to 10) at baseline. Furthermore, subgroup analyses were performed by investigational site.

Safety:

All safety analyses were performed on the Safety Set, which was comprised of all subjects allocated and treated with IMP. Analyses on the Safety Set was conducted according to the actual treatment received. All data were summarized by treatment. Baseline was defined as the last recorded observation before administration of IMP. Safety measures were summarized descriptively and listed.

Adverse events were coded to system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA). TEAEs were summarized for each treatment arm by SOC and preferred term. Additional summaries by intensity, relationship to IMP, outcome, and countermeasures were produced. Subjects with serious adverse events were summarized and listed. Special attention was given to subjects who discontinued treatment due to an adverse event or who experienced a severe adverse event or SAE. The incidence of TEAEs leading to premature discontinuation from treatment were presented descriptively. Adverse events of special interest (AESI) included nausea, vomiting, abdominal pain, gastrointestinal bleeding (preferred term: gastrointestinal haemorrhage), dizziness, and hypotension. All AESI data were descriptively summarized by treatment. TEAEs were also summarized by treatment for subgroups of age (< median, ≥ median), gender (male, female), race (mestizo, non-mestizo), baseline pain intensity (moderate, severe), concomitant medications (used, not used).

No post-enrollment clinical laboratory assessments were scheduled, and no post-allocation vital sign measurements were scheduled.

Summary of Results

Efficacy:

A total of 829 subjects were allocated to treatment in comparable proportions across the 4 treatment arms. Most subjects (>97%) in each treatment arm completed the study. One site contributed a higher number of subjects (41.0%) allocated to treatment compared to the other sites and likewise contributed a similar proportion of subjects to each analysis set. At least 99% of allocated subjects in each treatment arm were included in the Safety Set and FAS, and >88% of allocated subjects in each treatment arm were included in the PPS.

The demographic, dental surgical procedure and baseline pain intensity characteristics were similar between all 4 treatment arms. The population had a mean age of 23.6 years, and approximately two-thirds were female, and nearly all were Hispanic or Latino of mestizo race, with normal body systems upon physical examination. Most subjects (80.3%) had all 4 third molars extracted because they were impacted. Most subjects (>93.0%) from all treatment arms were compliant and received all 3 full doses of IMP.

Tramadol HCl/diclofenac sodium (Adorlan) 25 mg/25 mg (ADL 25/25) and tramadol HCl/diclofenac sodium (Adorlan) 50 mg/50 mg (ADL 50/50) combination therapy was more efficacious than D50 or T50 monotherapy. For all primary and secondary endpoints, the ADL 50/50 arm consistently showed significantly superior TOTPAR scores, SPID, time to onset of first perceptible pain relief, time to meaningful pain relief, 50% reduction in pain, and all exploratory endpoints as compared with T50 and D50 monotherapy. Moreover, the ADL 25/25 arm consistently showed significantly noninferior TOTPAR scores and superiority on all other parameters. The statistical conclusions drawn from the various imputation methods were consistent.

In the FAS, TOTPAR4 (least squares [LS] mean difference) scores showed significant noninferiority ($p<0.0001$, with delta of 1.5) with ADL 25/25 versus D50 and T50 and significant superiority ($p<0.0001$) with ADL 50/50 versus D50 or T50 monotherapy by LOCF with delta substitution imputation method for replacing missing values. Sensitivity analyses confirmed these results, regardless of the form of imputation. Furthermore, an ad hoc analysis indicated that ADL 25/25 achieved significant ($p<0.0001$) superiority versus D50 and T50 monotherapy (FAS) according to the LOCF with delta substitution imputation method for replacing missing values. For subgroup analyses of both moderate and severe baseline pain intensity, TOTPAR4 results showed significant noninferiority ($p<0.0001$, with delta of 1.5) with ADL 25/25 versus D50 and T50 and significant superiority ($p <0.0001$) with ADL 50/50 versus D50 or T50 monotherapy (FAS) according to the LOCF with delta substitution imputation method for replacing missing values.

All TOTPAR6 and TOTPAR8 (LS mean difference) scores showed significant noninferiority ($p<0.0001$, with

delta of 1.5) with ADL 25/25 versus D50 and T50 and significant superiority (p <0.0001) with ADL 50/50 versus D50 or T50 monotherapy. Sensitivity analyses for TOTAR 6 and TOTPAR8 corroborated these data according to the LOCF with delta substitution imputation method for replacing missing values. Sensitivity analyses confirmed these results.

PID scores continued to improve with increasing time from baseline to 24 hours posttreatment in all treatment arms. The SPID scores (LS mean differences) indicated that ADL 25/25 achieved noninferiority and ADL 50/50 achieved superiority versus D50 and T50 monotherapy at each timepoint.

The time to onset of first perceptible pain relief and time to meaningful pain relief were reached substantially more rapidly by subjects who received combination therapy versus D50 and T50 monotherapy.

A 50% reduction in pain from baseline was achieved earlier with combination therapy versus D50 and T50 monotherapy, less than half the time in the ADL 50/50 arm. Moreover, the number of subjects censored was higher in the D50 and T50 treatment arms because more subjects required rescue medications, an indication of less satisfactory pain relief in the monotherapy groups. Further corroboration of these data indicated that the time to intake of rescue medication was earlier and more frequent with monotherapy versus combination therapy.

For all treatment arms, the percentages of very good or excellent scores combined in the subject's global evaluation of treatment were more favorable at 24 hours than after 8 hours, with the highest percentage of very good and excellent scores in the combination therapy arms.

All exploratory endpoints of scores of pain relief, pain intensity, PID, peak and time to peak PID peak and time to peak pain relief, and time to first rescue medication, favored combination therapy versus monotherapy with the most efficacious treatment achieved by the ADL 50/50 arm.

Safety:

The safety profile of the ADL combination therapy (25/25 and 50/50) was consistent with the known safety profile of the comparator products (D50 and T50). No unexpected findings were observed.

The D50 and ADL 25/25 treatment arms had a lower incidence of TEAEs and treatment-related TEAEs compared to the T50 and ADL 50/50 treatment arms when subjects were exposed to higher doses of tramadol (TEAEs: 23.2% and 30.2% versus 51.0% and 46.2%, respectively; treatment-related TEAEs: 4.8% and 11.2% versus 31.1% and 23.6%, respectively).

The most commonly reported TEAEs (>10% of subjects) of nausea, vomiting and dizziness were known adverse drug reactions to diclofenac and tramadol, and occurred in the T50, ADL 25/25 and ADL 50/50 treatment arms. None of the TEAEs reported in the D50 treatment arm had an incidence >10%. Treatment arms consisting of higher doses of tramadol, T50 and ADL 50/50, had more than twice incidence of nausea, vomiting and dizziness than that of D50 and ADL 25/25 (nausea: 25.2% and 24.5% versus 3.4% and 7.3%; vomiting: 21.4% and 19.7% versus 1.4% and 5.9%; dizziness: 14.1% and 12.0% versus 2.9% and 5.4%, respectively). The higher incidence of known adverse drug reactions in subjects exposed to T50 and ADL 50/50 was in line with the known safety profile of tramadol and with higher exposure in these treatment arms. Procedural pain was also a commonly reported TEAE, with verbatim terms indicating all incidences were associated with the original oral surgical procedure.

In general, most TEAEs of nausea, vomiting, and dizziness occurred on Day 1 while subjects were receiving IMP, and most were considered related to IMP or rescue medication by the investigators.

Severe TEAEs occurred in <3.0% of subjects in any treatment arm. All severe nausea and vomiting events occurred in the T50 and ADL 50/50 arms, and all severe dizziness events occurred in the ADL 50/50 arm in accordance with higher exposure to tramadol in these treatment arms.

Females reported TEAEs more commonly than males, which included overall TEAEs (42.5% versus 29.0%), and the most common TEAEs of nausea (18.9% versus 8.4%), vomiting (16.4% versus 4.4%), and dizziness (10.2% versus 5.7%). This finding was not unexpected considering known gender differences in reporting opioid adverse drug reactions. No other notable differences were observed among the treatment arms for the other subgroups of age, race, baseline pain intensity, and concomitant medication use.

No deaths and 1 treatment-emergent SAE of seizure (ADL 25/25) was reported during the study (severe, possibly related). Treatment-emergent AEs led to discontinuation of IMP in <2.0% of subjects in any treatment arm, all of whom had at least 1 gastrointestinal disorder of nausea and/or vomiting. One possible exception was seizure that did not result in discontinuation on the AE CRF, but was marked as resulting in discontinuation on the disposition CRF.

As with overall TEAEs, the incidence of select TEAEs of nausea, vomiting, dizziness, hypotension, abdominal pain, and gastrointestinal haemorrahge in the T50 and ADL 50/50 treatment arms was more than twice that observed in the D50 and ADL 25/25 treatment arms (37.4% and 32.7% versus 6.3% and 12.7%, respectively). Select TEAEs were mostly comprised of nausea, vomiting and dizziness, and none were serious.

CONCLUSIONS

The results of this postoperative pain study indicate that ADL 25/25 and ADL 50/50 combination therapies are complementary and provide superior beneficial analgesic effects versus diclofenac 50 mg and tramadol 50 mg monotherapies after third molar extraction. The safety profile of the ADL combination therapy (25/25 and 50/50) was consistent with the known safety profile of the comparator products (D50 and T50). ADL combination therapy provided significantly superior beneficial analgesic effects across all efficacy measures at no greater risk compared to diclofenac and tramadol monotherapies.

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