LETTER TO THE EDITOR

METHODOLOGICAL ISSUES ON A CLINICAL TRIAL TO TEST TAPENTADOL PROLONGED RELEASE VS. OXYCODONE/NALOXONE PROLONGED RELEASE

To the Editor:

A recent article by Baron et al.[1] reports the results of a clinical trial (CT) to compare the effectiveness of tapentadol with oxycodone/naloxone (Ox/Nal) for the treatment of chronic low back pain of neuropathic origin. This study is a remarkable attempt to progress in this area. We argue, however, that it contains several drawbacks that leave open ground for further trials with more stringent methodological controls.

The double-blind design: The preventive effect of double-blinding against the effects of placebo and nocebo has been extensively documented in the literature. The decision to perform an open-label trial runs contrary to the basic rules of CTs.

The use of pickup arms: Using "pickup or rescue arms" prevents the evaluation of the superiority of one treatment over another. In the reviewed trial, there are other reasons that render the use of a rescue arm doubly questionable: The first is the asymmetry which allows to use tapentadol under some subjective conditions of lack of efficacy of Ox/Nal, but not the other way around; the second is that the use of this "rescue arm" is combined with the open-label design and prior information to the patient. This leads to unmanageable biases when combined with the use of prior treatments without full equipoise.

Dynamics of titration: In CTs aimed at comparing drugs, it is essential to consider pharmacokinetic characteristics of the drugs. In the evaluated study, the comparison was not performed according to this principle because the administration of Ox/Nal did not comply with the established guidelines neither in dose titration nor in titration intervals. They were however adapted to tapentadol guidelines.

Criteria for continuation or discontinuation during titration period: The literature favors the use of validated numerical scales sensitive to changes in chronic pain intensity.[2,3] The use of these scales requires a rigorous control of reproducibility. In the reviewed study, two alternative criteria were formulated to enter the maintenance period, which are based essentially on the same metric, although with different cutoff points. In any case, it is essential to report the quantitative pain reduction achieved up to that point in each trial arm.

On the inclusion criteria: The selection of patients not previously exposed (naïve) to the use of opioids is a logical criterion. On the same ground, we wonder why the protocol allowed to select patients under treatment with co-analgesics, with lower levels of pain than the rest of patients and with a negative score in the scale painDETECT.

The use of the last observation carried forward (LOCF) for imputing the missing data: This method is based on the assumption that the time series is stationary, which does not appear to be a realistic assumption in this trial because it entails the assumption that the patient's perception of change remains constant.

CONCLUSIONS

The evidence derived from this trial supports the feasibility of the use of both drugs, but is so far insufficient for an excluding preference for one or the other.

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CONFLICT OF INTEREST

This letter was written by the authors on a proposal from Mundipharma Spain; Mundipharma did not participate in the preparation of the letter.

REFERENCES

1. Baron R, Likar R, Martín-Mola E, et al. Effectiveness of tapentadol prolonged release (PR) compared with oxycodone/naloxone PR for the management of severe chronic low back pain with a neuropathic component: a randomized, controlled, open-label, Phase 3b/4 study. *Pain Pract*. 2015. DOI. 10.111/papr.12308. [Epub ahead of print].

2. Management of Opioid Therapy for Chronic Pain Working Group. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain*. Washington, DC: Department of Veterans Affairs DoD; 2010.

3. Breivik EK, Skoglund LA. Comparison of present pain intensity assessments on horizontally and vertically oriented visual analogue scales. *Methods Find Exp Clin Pharmacol*. 1998;20:719–724.

IN RESPONSE:

To the Editor:

In response to the Letter to the Editor, we will substantiate point-by-point why our study is appropriate and supportive of the favorable efficacy and tolerability profile of tapentadol prolonged release (TAP). Our study was designed to test the hypotheses of noninferiority (followed by superiority) for TAP vs. oxycodone/naloxone PR (OXN) in a preplanned, 2-step statistical testing procedure for two co-primary endpoints.[1,2] The study hypotheses assumed an efficacy of OXN

comparable to that of oxycodone CR (OXY)[3] and a difference in tolerability of OXN vs. OXY related to naloxone's (nonsystemic) effect on opioid-induced constipation. As per relevant EMA guideline,[4] the criteria for switching between noninferiority and superiority were met (lower boundary of the 97.5% RCI of the difference not including zero). As a result, the trial provided confirmatory evidence of superiority of TAP vs. OXN.

1. *Open-label vs. double-blind study design*: Efficacy and safety of TAP vs. OXY has already been established in three large double-blind RCTs in osteoarthritis and low back pain.[5,6] A preplanned, pooled analysis of these trials showed superiority of TAP over OXY for the primary efficacy endpoints, validated quality-of-life parameters, and gastrointestinal tolerability.[7] With this level of evidence already established, it is appropriate to collect more "real-world" data. Evidence derived from such "real-world"/"pragmatic" effectiveness RCTs fulfills the criteria for evidence level Ib according to evidence-based medicine standards like those of the Cochrane Collaboration. In addition, open-label trials are accepted by regulatory and Health Technology Assessment (HTA) agencies to complement evidence derived from double-blind RCTs and to overcome associated limitations (eg, selected populations, less practice-related settings). Therefore, the open-label design of this trial can be considered appropriate.
2. *Pickup arm*: The pickup arm had a scientific and ethical rationale. TAP has shown superior efficacy over OXY (active component of OXN) proposed to be linked to its 2 mechanisms of action (MOR-NRI) in large, double-blind RCTs.[8] Additionally, TAP was superior to OXY not only on constipation (where OXN might be favorable vs. OXY), but also on other GI side effects.[7] The pickup arm was intended to provide patients with a fair chance to achieve pain relief with acceptable tolerability, a setting that can be considered a reflection of clinical practice; in contrast, a switch from TAP to OXN was (evidence-based) unlikely to provide additional benefits. Would this approach have introduced relevant bias? The discontinuation rate with OXN in the present study (62.5%) was comparable to that with OXY (61.7%) in large-scale, double-blind, phase III RCTs which did not include pickup arms.[7] This indicates that the pickup arm did not significantly influence discontinuation rates.
3. *Dynamics of titration*: Referring to both prescribing information (PI) as the relevant guidelines for treatment initiation and maintenance, the titration regimen used can be considered fair and adequate in the context of the trial setting and objectives. It allowed for dose increases at an equianalgesic ratio, thereby avoiding bias due to underdosing of one compound in cases of unequal dose steps. According to international prescribing information, OXN may be titrated in steps of 10/5 mg bid as done in our trial and potentially faster (every 1–2 days[9,10]). But it is unlikely that prolonging the titration steps by 1 day causes any relevant bias. Furthermore, it addresses the needs of a sensitive, non–opioid-pretreated population, which is highly susceptible to opioid side effects such as nausea and vomiting. If the slower titration (every 3 days) led to bias, this could only have been due to lack of efficacy. During the titration phase, only 16.6% of dropouts in the TAP arm and 18.8% in the OXN arm were due to lack of efficacy, which strongly argues against a bias due to prolongation of the titration interval by 1 day.
4. *Response criterion for the titration phase:* There were 2 alternative criteria to enter the continuation phase of the study: The first required a pain intensity ≤ 4 (on the well-established NRS-3) with acceptable tolerability at the end of titration; the second was meant to offer a fair chance to patients to continue treatment if pain was reduced to ≤ 5 at the highest tolerated dose and continuation was justifiable. The quantitative pain reduction achieved up to that point in the full analysis set, as requested by the authors of the letter, is published in our article (figure 5)[1] with −3.4 and −2.5 for TAP and OXN, respectively.
5. *Inclusion criteria:* This study was intended to evaluate treatment responses in patients with pain with a neuropathic component.[1] As opioid monotherapy is often insufficient for the treatment of neuropathic pain, co-analgesics are frequently added. Excluding patients taking co-analgesics could have led to selection of patients with mild neuropathic symptoms. Pain (NRS) and PainDETECT scores in these patients were allowed to be slightly lower at enrollment due to the use of co-analgesics, expecting that scores would rise after their mandatory washout and they had to be ≥ 6 (for NRS) and "unclear" (PainDETECT) at randomization (baseline) for all patients.
6. *Imputation:* The use of any type of imputation or no imputation represents a form of bias. As per the EMA guidance for missing data, there is no universally applicable method of handling missing data.[11] The imputation method was fully prespecified at the beginning of the trial. The choice of using LOCF is based on the fact that this method was widely used for assessing the efficacy in pain, it provides a pragmatic and reasonable conservative imputation method, and it is used in previous TAP trials, thus allowing comparability of the trial results.

We maintain that this trial taken together with other data available on TAP supports its favorable efficacy and tolerability profile.

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REFERENCES

1. Baron R, Likar R, Martin-Mola E, et al. Effectiveness and safety of tapentadol prolonged release (PR) compared with oxycodone/naloxone PR for the management of severe chronic low back pain with a neuropathic component: a randomized, controlled, open-label, phase 3b/4 study. *Pain Pract*. 2015; doi: 10.1111/papr.12308. [Epub ahead of print].

2. Baron R, Jansen JP, Binder A, et al. Tolerability, safety, and quality of life with tapentadol prolonged release (PR) compared with oxycodone/naloxone PR in patients with severe chronic low back pain with a neuropathic component: a randomized, controlled, open-label, phase 3b/4 trial. *Pain Pract*. 2015; doi: 10.1111/papr.12361. [Epub ahead of print].

3. Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain*. 2008;9:1144–1154.

4. Committee for Proprietary Medicinal Products (CPMP). Points to consider on switching between superiority and non-inferiority. *Br J Clin Pharmacol*. 2001;52:223–228.

5. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother*. 2010;11:1787–1804.

6. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*. 2010;30:489–505.

7. Lange B, Kuperwasser B, Okamoto A, et al. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. *Adv Ther*. 2010;27:381–399.

8. Sanchez del Aguila MJ, Schenk M, Kern KU, Drost T, Steigerwald I. Practical considerations for the use of tapentadol prolonged release for the management of severe chronic pain. *Clin Ther*. 2015;37:94–113.

9. PI Targiniq ER 07/2014, Reference ID: 3598302

10. German Summary of Product Characteristics Targin® 05/2014.

11. Flyer P, Hirman J. Missing data in confirmatory clinical trials *J Biopharm Stat*. 2009;19:969–979.