

Development issues related to designs in neuropathic pain in light of the European Medicines Agency's (EMA) Guideline for the treatment of pain

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Abstract

In this paper, we review certain aspects of the new guideline on the clinical development of medicinal products intended for the treatment of pain of the European Medicines Agency, which came into effect July 2017. The content the new guideline seems to be especially of value for the development of oral or parenteral analgesics, and is less relevant for topical formulations, which increasingly are recognized as important new therapeutic modalities for neuropathic pain. The guideline discusses the importance of targeting the population, and points out that new, innovative development designs are welcomed. We will present aspects of such designs. Cross-over studies, enrichment and withdrawal designs are discussed, and for the development of a topical analgesic, the latter study designs are better fit to capture clear efficacy versus placebo. For repurposing of old drugs in the field of pain, consultation with competent authorities (national or centrally via EMA) is advised, to discuss in depth what is required to obtain a marketing authorization for an old repositioned drug on a case-by-case basis.

Introduction

On the 1st of July 2017, the new guideline on the clinical development of medicinal products intended for the treatment of pain of the European Medicines Agency came into effect. The guideline provides guidance for the clinical development of new medicinal products for the treatment of pain, and replaces the earlier guidelines on neuropathic (CPMP/EWP/252/03) and nociceptive pain (CPMP/EWP/612/00). Given its content the new guideline seems to be especially of value for the development of oral or parenteral analgesics, and less relevant for topical formulations. In the latter case, only transdermal formulations are mentioned, and no reference is made to topical formulations of a different class (epidermal formulations). Also, the guideline does not contain specific recommendations for transdermal formulations.

The guideline mentions that it is specifically applicable for New Medicinal products; these are not defined in the guideline or in the glossary of the EMA [1]. 'Medicinal products' are defined in the glossary as: 'A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action' [2]. We can interpret 'new' in such a way that it refers to a New Chemical Entity (NCE) rather than to a line extension of an existing drug. There is support for this interpretation in the aforementioned guideline on pain, as on page 15 the guideline refers to: 'data requirements for new active substances'.



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The guideline therefore does not explicitly cover repositioned old drugs and line-extensions of existing analgesics. As there are no specific guidelines in place for repositioned drugs, we will review 2 key recommendations of the guideline in the light of 'old' repositioned drugs. The authors are closely involved in the development of topical phenytoin, via an investigator driven development plan [3]. This involvement provided the base for an in-depth review of these 2 aspects of the guideline on pain and we present some commentaries within the above context of the development of a repositioned drug (phenytoin), in a new formulation (topical cream) for the treatment of Painful Diabetic Neuropathy (PDN).

The first item we would like to discuss is the relationship between pathogenic mechanisms, mechanism of action and the selection of the target population; the second item relates to the design of the studies to support this investigator driven repositioning project.

Repurposing old drugs: a strong need for an investigator driven development

Drug repositioning or repurposing is a dynamic field of drug development that can offer additional benefits to patients, suffering from disorders without adequate treatment options, such as patients with neuropathic pain. Drug repositioning refers to the process of finding new uses for existing drugs outside the scope of the originally authorized medical indication. It can also relate to new formulations and/or routes of administration of old drugs in new indications. One key obstacle for the registration of drugs outside their authorized indication, not recognized by many, is the fact that old drugs are off-patent and therefore pharmaceutical industries in general will not invest in developments for new indications (in new formulations) for these old drugs, in the absence of clear financial incentives for such development. Developing an old drug in a new indication therefore needs to be taken into the hands of non-commercial investigators, who, based on external regulatory advice and after consultation with competent authorities, can become the designers of such a development plan. In this context of an investigator driven development, we will analyze the two aspects mentioned above as described in the recent new EMA guideline on pain.

Heterogeneity tends to reduce the trial's chance of success

The objective of the guideline is 'to provide guidance on clinical studies that are feasible and likely to produce interpretable results' (p. 4/29). This objective is extremely important, as we have seen recently an increasing number of clinical trials in the field of neuropathic pain where the results were negative or non-conclusive.

The guideline points out that in chronic pain 'multiple and complex mechanisms are frequently involved' (p 16). It is also stated that 'heterogeneity tends to reduce the trial's chance of success' (p. 11). The guideline is quite specific where it states that 'Better characterization of the mechanisms predominant in each individual patient and the tailoring of specific therapies accordingly, could in principle result in greater therapeutic success than has been achieved to date in the treatment of chronic pain' (p.16). Indeed, one of the main scientific reasons for failed studies most probably can be found in the unrecognized heterogeneity of the included patient population. The guideline highlights the importance of this topic in separate paragraphs (pp 11,14 and 20).

In chapter 5.1.2. Under the header 'pharmacodynamics' the guideline refers to the exploration of phenotypic (and pharmacogenomic) aspects to identify patients more likely to respond to agents with specific mechanisms of action. In chapter 6 (introduction) the ideal situations is described for a general analgesic that is effective in the whole range of pain conditions. The guideline points out that taking into account the increasing knowledge about diverse mechanisms underlying different pain conditions, this situation is not likely to be achievable for new active substances developed for the treatment of pain.

In chapter 6.2.1. The guideline stipulates the importance of the development of new medicinal products which may increasingly be targeted at particular subgroups of patients for whom the mechanism of action of the new medicine is most suited (p.16).

As heterogeneity in the selected trial population reduces the trial's chance of success, the guideline recommends that efficacy should be studied in a trial population that is homogenous with respect to diagnosis and pain intensity. When we translate this to neuropathic pain, recent diagnoses in that field are debated in the guideline as missing such homogeneity. The category chronic idiopathic axonal neuropathy (CIAP), cryptogenic sensory peripheral neuropathy (CSPN) and Small Fiber Neuropathy are categories which overlap considerably. As the etiology of all these diagnoses remains unknown, the pathogenesis might be different too. In etiologically defined peripheral neuropathies, such as in Post Herpetic Neuralgia (PHN) heterogeneity still may play a role. Although recent data support uniformity in etiology in PHN, at least 3 different pathogenetic and symptomatic subgroups are described in PHN:

1. Patients with irritable nociceptors presenting stimulus-evoked symptoms of mechanical allodynia and thermal hyperalgesia;
2. Patients with differentiation presenting spontaneous pain and partial sensory deficits;
3. And patients with central reorganization presenting mechanical allodynia and sensory deficits [4].

Furthermore, it is also not fully clear what type of sodium channels play the major pathogenetic role in the nociceptors of patients with

PHN. Six of 9 channels are most probably relevant on the nociceptor and the keratinocytes and thus a high selective sodium channel blocker, for instance targeting the NaV1.7 channel only, would seem to be a suboptimal choice [5].

If one of the major pathogenetic disturbances in the skin in the above mentioned peripheral painful neuropathies are the sodium channels, one can easily understand that topical treatment using gabapentin (a centrally acting alpha-2 delta-1, calcium channel blocker) as the active compound might lead to non-responders [6].

In chapter 6, related to confirmative studies, the guideline once more highlights that such studies should be performed in essentially homogeneous patient populations (p.14). This can be seen as an implicit welcoming of enrichment designs in phase III studies (see below).

Cross-over, parallel and enrichment studies

Related to trial designs, it is pointed out that the design of clinical trials is a complex and rapidly developing area. A number of designs are mentioned and discussed, and it is pointed out that the clinical data package to support a particular indication of a repurposed drug depends on the extent to which efficacy data can be extrapolated across pain models and populations, taking into account the known properties of the drug. It is therefore not possible according to the guideline, to define exact data requirements (number of trials, number of different pain models etc.) for all anticipated scenarios (p.17).

The guideline stresses that in general a randomized, controlled, parallel group trial is the most appropriate design for confirmatory evidence of efficacy in pain trials.

Due to the dynamic nature of clinical trial design science in chronic pain, the guideline creates space for more innovative approaches. It is pointed out that such designs are especially welcomed for studies including patients with severe and difficult to treat chronic pain. If development favors such approaches the guideline recommends to seeking scientific advice from National Competent Authorities and/or the EMA/CHMP.

For explorative studies, cross-over designs minimizing carry over effects are acceptable in case of stable pain symptomatology (p.9). This is once more referred to in the chapter on breakthrough pain, where the guideline states: 'cross over designs in which each patient serves as his/her own control may be applicable when analgesic requirements are reasonably stable' (p.21).

Randomized withdrawal studies are mentioned as a possible approach in chronic pain. Clearly this design was implemented in the phase II and III studies of the lidocaine plaster.

Enriched enrolment strategies are also indicated to be acceptable at the explorative phase of drug development. Further, in chapter 6 there was a clear emphasis on confirmatory efficacy studies, which should be performed in essentially homogeneous patient populations (p.14). This could be achieved through enrichment in suitable situations, such as neuropathic pain, where the symptoms are symmetrical. Thus, the patients can be their own control in separating responders from non-responders.

Conclusion

The aim of the recent EMA guideline on pain is to present guidance for how to develop a new medicinal product in the various

pain syndromes. Neuropathic pain is also covered in this guideline, both peripheral as well as centrally originated neuropathic pain. The guideline does not mention topical analgesics, apart from a brief reference to transdermal formulations. Formulations aimed for the nociceptors in the skin only, and based on an intra-dermal mechanism of action are not referred to in the guideline and clearly are not its focus, nor is the guideline written to assist development of repositioned drugs. Yet, the guideline is our best point of reference in preparing a development plan for a repurposed substance. In a number of paragraphs, the guideline discusses the need to find a closer fit between mechanism of action and pathogenesis of the various pain states. It discusses the importance of targeting the population from the above perspective, and points out that new, innovative development designs are welcomed. Among such designs cross-over studies, enrichment and withdrawal designs are presented. For the development of a topical analgesic, the latter study designs are better fit to capture clear efficacy versus placebo. For repurposing of old drugs in the field of pain, consultation with competent authorities (national or centrally *via* EMA) is advised, to discuss in depth what is required to obtain a marketing authorization for an old repositioned drug on a case-by-case basis. Given the fact that old drugs are off-

patent, such support is especially important in the execution of investigator driven development [3]. To facilitate this, both EMA and several national authorities provide significant fee reductions on Scientific Advice procedures for small businesses and/or non-commercial groups.

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