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Kappa Receptors Agonist in Postoperative Pain

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Abstract

The peripherally acting kappa receptors agonist CR845 (difelikefalin) is currently in late development by Cara Therapeutics, for the treatment ofuremic pruritus, post-operative pain and pain in osteoarthritis. The principle of treating pain via a peripheral acting opioid, is supposed to have special advantages, among which the absence of central opioid side effects, and has actually been defined already in the last century. Phase I development of CR845 started in 2008, phase II studies have been completed, and phase III is ongoing for two formulations: an intravenous formulation for postoperative analgesia and uremic pruritus, and an oral formulation for treatment of chronic pain in osteoarthritis. However, as primary scientific data on CR845 in peer reviewed journals to date are absent, we can only evaluate the documents produced by the company, among which press releases of CARA Therapeutics, presenting results of a number of preclinical and clinical studies. We present a profile of CR845 based on this information, especially since CR845 is first in class and the principle seems to holds promises for the treatment of pain and itch.

Introduction

Peripheral kappa receptor agonists for pain

There is an ongoing intense debate about pros and cons of prescription of opioids, and it is clear that less or non-addictive opioids would be greatly welcomed. Peripherally acting opioid agonists may be such analgesics. The potential advantages of kappa receptor agonists restricted to the peripheral nervous system are outlined already [1].

There are a number of such compounds in development, such as asimadoline (EMD-61753), D-Arg2, Lys4-Dermorphin-(1-4)-amide (DALDA), enadoline, TRK-820, U50488, ICI-204,448and FE200665 and families of compounds based on certain scaffolds in the laboratory, such as tetrahydroisoquinoline quaternary derivatives. TRK-820 is a peripheral kappa receptor agonist from Toray Industries, Inc., also known as nalfurafine, and is available in Japan and registered since 2009 for the treatment of uremic pruritus, one of the current development indications for CR845 [2]. Naloxegol is available since 2014 in the USA as a once-daily oral therapy indicated for the treatment of opioid-induced constipation.

CR845 originating from the Swiss company Ferring Pharmaceuticals and the compound is also known as CKD-943, FE 202845 and MR13A9. A prototype of this drug was well tolerated in humans, with no reports of dysphoria or hallucinations, and as effective as oxycodone in a human model of acute visceral pain [3]. However, the preclinical profile was suboptimal due to low orally bio available. CR845 was positioned as a second-generation peptide, orally bio available, and CARA reported to have completed Phase I clinical trials in 2009 [4]. The intravenous formulation is in phase III development for postoperative pain and uremic pruritus. The oral formulation for the treatment of chronic pain in phase II.

Publications on CR845 in peer reviewed articles

In addition to company press releases we could find only3published posters on the compound [5-7]. In addition we identified two book chapters (the same chapters, written by the same authors), published in 2015, without giving additional details [8,9]. The first poster presented data from an un blinded, pooled treatment-emergent adverse events analysis, based on in a total of 368 patients, from 3 double-blind, randomized, placebo-controlled, Phase 2 clinical studies. The second poster presented the preclinical profile of the drug, and the last poster, presented the results of a phase II bunionectomy study.

Preclinical profile

The preclinical profile is described in a company poster: 'Preclinical Profile of CR845: A Novel, Long-Acting Peripheral Kappa Opioid Receptor Agonist', presented at the IASP in 2008 [10]. CR845 is presented as highly selective kappa agonist, without off-target. In various pain paradigms CR845 dose

dependently inhibited pain behavior. In the acetic acid induced writhing in male mice 0,01, 0,03, 0,1 and 0,3mg/kg IV were tested versus vehicle and ED50 was 0.07mg/kg IV. In an abdominal pain model ED50 was 0.3mg/kg IP or IV. In a pain-inflammation model 0.3 and 1mg/kg were significantly better than vehicle. In a neuropathic pain model ED50 was 0.38mg/kg IV. In an itch model, 48/80 or 5'GNTI induced pruritus, CR845 0,1 and 0,3mg/kg significantly inhibited scratch behavior, ED50 = 0.08mg/kg IV.

Early studies

All the data are based on press releases on the CARA company website. Apr 28, 2008 CARA announced the initiation of its I.V. phase I program, and defined the compound as: "long-acting peripheral kappa opioid receptor agonist". On August 5, 2008, the results of a phase I study, evaluating the IV formulation, was presented at the company's website [11]. In a double-blind, randomized, placebo-controlled, single escalating intravenous dose study was evaluated in 54 healthy male and female volunteers, and the results showed linear, dose-proportional increases in systemic exposure to CR845. CR845 infusion also was said to trigger surrogate markers for peripheral kappa opioid receptor activation. Phase I data of the oral formulation were communicated on April 3, 2012, and a robust bioavailability and pharmacologic activity was reported for the oral formulation [12]. On February 8, 2010, the company announced further positive phase II data for in postoperative pain, and significant pain relief was observed in CR845-treated patients over placebo, more details were given in 2012 [13].

Further phase II study

In 2013 the company presented the results of a phase II study in the treatment of pain following bunionectomy [14]. In the complete analysis an I.V. 0.005mg CR845/kg/dose CR845, resulted in significantly greater pain reduction than placebo In 2015 CARA presented results from a double-blind, randomized, placebo-controlled trial in 65 dialysis patients, active drug reduced itch significantly compared to those receiving placebo. In the same year Cara announces positive results osteoarthritic pain knee or hip, based on a multiple ascending dose trial in 80 patients: 0.25mg, 0.5mg, 1.0 mg and 5.0mg, dosed twice a day during a two-week period. Half of all patients in the 5.0mg dose group reported at least a 30 percent reduction in their pain score at the end of the treatment period).The company also reported dose-proportional PK effects in the 1 and 5mg range.

Conclusion

The new peripheral acting kappa opiate agonist CR845 has been evaluated within the company CARA for a period of 9 years since first start of development in 2008. The data communicated therefore has to be interpreted given the conflict of interest of the company and her representatives. Based on the company information reviewed however, the profile of the drug seems quite interesting: CR845 is a small peptide molecule, without penetration in the central nervous system, effective against acute, post-surgical pain and in osteoe arthrosis pain, with some side effects, such as facial tingling or numbness, dizziness and fatigue. Human abuse liability (HAL) study does not raise red flags, and there seems to be no negative effects of respiratory depression. This is in line with separate analysis of this group of compounds [15].

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