Kappa Receptors Agonist in Postoperative Pain

Jan M Keppel H*
Department of molecular pharmacology, University of Witten/Herdecke, Germany
Submission: February 22, 2017; Published: September 12, 2017
*Corresponding author: Jan M Keppel Hesselink, Department of molecular pharmacology, University of Witten/Herdecke, Germany, Email: jan@neuropathie.nu

Abstract
The peripherally acting kappa receptors agonist CR845 (difelikefalin) is currently in late development by Cara Therapeutics, for the treatment of uremic 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-204,448 and 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 only 3 published 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 unblinded, 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
Kappa Receptors Agonist in Postoperative Pain. J Anest & Inten Care Med. 2017; 3(4) : 555620.

Penetration in the central nervous system, effective against quite interesting: CR845 is a small peptide molecule, without the company and her representatives. Based on the company therefore has to be interpreted given the conflict of interest of been evaluated within the company CARA for a period of 9 years. Conclusion at the end of the treatment period). The company also reported group reported at least a 30 percent reduction in their pain score during a two-week period. Half of all patients in the 5.0mg dose patients: 0.25mg, 0.5mg, 1.0 mg and 5.0mg, dosed twice a day pain knee or hip, based on a multiple ascending dose trial in 80 osteoarthritic 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 osteoarthritis 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].

References
1. Barber A, Bartoszyk GD, Bender HM, Gottschlich R, Greiner HE, et al. (1994) A pharmacological profile of the novel, peripherally-selective κ-opioid receptor agonist, EMD 61753. Br J Pharmacol 113(4):1317-1327.
2. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, et al. (2010) Effect of a novel kappa-receptor agonist, nafurafine hydrochloride, on severe itch in 337 haemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant 25(4): 1251-1257.
3. Arendt-Nielsen, Lars (2009) "Analgesic Efficacy of Peripheral κ-Opioid Receptor Agonist CR665 Compared to Oxycodone in a Multi-modal, Multi-tissue Experimental Human Pain Model Selective Effect on Visceral Pain." The Journal of the American Society of Anesthesiologists 111(3): 616-624.
4. Aldrich JV, Jay PM (2009) "Peptide kappa opioid receptor ligands: potential for drug development?" The AAPS journal 11(2): 312-322.
5. Joseph WS, Paul DO, Tiseo J, Frédérique M, Robert H, et al. (2015) CR845, A Novel Peripherally-Acting Kappa Opioid Receptor Agonist, Provides Post-Operative Analgesia as Well as Reduces Post-Operative Nausea and Vomiting. Poster presented at American Society of Anesthesiologists, Poster A 3209.
6. Luis RG, Robert HS, Derek TC, Frédérique M (2008) Preclinical Profile of CR845: A Novel, Long-Acting Peripheral Kappa Opioid Receptor Agonist. Poster PW-231 presented at IASP.
7. Menzaghi F, Spencer R, Abrrouk N, Lewis M, Chalmers D (2015) CR845, a peripheral kappa opioid, provides better pain relief with less nausea and vomiting than placebo in patients after bunionectomy. The Journal of Pain 16(4): S81.
8. Cowan A, Kehner GB, Inan S (2015) Targeting Itch with Ligands Selective for κOpioid Receptors. Handb Exp Pharmacol 226:291-314.
9. Cowan A, Kehner GB, Inan S (2015) Targeting Itch with Ligands Selective for κOpioid Receptors. In: Alan Cowan, GilYosifovitch (Eds.), Pharmacology of Itch. Springer pp. 291-314.
10. Luis RG, Robert HS, Derek TC, Frédérique M (2008) Preclinical Profile of CR845: A Novel, Long-Acting Peripheral Kappa Opioid Receptor Agonist. Poster PW-231 presented at IASP.
11. CARA therapeutics: Cara Therapeutics Announces Successful Completion of Phase I Clinical Trial of Novel Analgesic.
12. CARA therapeutics. Cara Therapeutics Successfully Completes Phase I Study With Oral Formulation Of Its Novel Kappa Opioid Receptor Agonist, CR845.
13. (2012) CARA therapeutics. Cara Therapeutics Reports Positive Results from Phase II Trial Of Novel Peripheral Kappa Agonist, CR845, in Acute Post-Operative Pain. Shelton, CT | JUNE 11, Cara Therapeutics Reports Positive Results from Phase 2 Clinical.
14. Trial of Novel Peripherally-Acting Kappa Opioid Receptor Agonist, I.V. CR845, for Post-Operative Pain Following Bunionectomy.
15. Albert VA, Boyd MR, Hall AL, Morgado SJ, Nguyen E, et al. (2016) Will peripherally restricted kappa-opioid receptor agonists (pKORAs) relieve pain with less opioid adverse effects and abuse potential? J Clin Pharm Ther 41(4): 371-382.
