The new analgesic CR4056 effectively abrogates neuropathic pain induced by Bortezomib in rats

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Objective: Bortezomib, a potent and selective proteasome inhibitor, is the first line treatment of relapsed, refractory multiple myeloma. One of the most commonly reported adverse reactions induced by this drug, is a peripheral neurotoxicity characterized by sensory and often painful neuropathy representing the major reason for a dose reduction and discontinuation of life-saving therapy. The use of currently available drugs for the treatment of neuropathic pain is largely empirical, and their mechanisms of action are not completely understood. CR4056 is a promising analgesic drug that interacts with imidazoline-2 receptors, and inhibits the activity of monoamine oxidases. Aim of this study was to evaluate if the new analgesic compound CR4056 could prevent (preventive schedule) or reverse (curative schedule) the neuropathic pain elicited by bortezomib in a rat model of chronic painful peripheral neuropathy .

Methods: Neuropathy was induced in female Wistar rats by intravenous administration of Bortezomib (0.20 mg/kg, 3 times a week). CR4056 was orally administered at 6 mg/kg, once a day, in both preventive and curative schedules. In the preventive schedule animals were dosed with bortezomib and CR4056 starting from day 1 till week 8 or 10. In the curative schedule, established neuropathic animals were treated with CR4056 either from week 6 or week 8 till week 10. The sensory neuropathy was evaluated by tail nerve conduction velocity (NCV) at week 6, 8 and 10 after the first challenge with bortezomib. The development of neuropathic pain behaviour (mechanical allodynia) was followed by mechanical testing on day 1, at week 6, 8, 9 and 10. General toxicity, evaluated as body weight changes, was monitored twice a week

Results: Bortezomib induced a severe reduction in NCV and a significant mechanical allodynia at all the indicated time points. Administration of CR4056, neither in preventive nor in curatives schedules, affected the NCV impairment. Conversely, CR4056 treatment significantly and completely prevented the development of mechanical allodynia in bortezomib treated-rats, in the preventive schedule, and totally reverted the established neuropathic pain in the curative schedule. The analgesic effect persisted until the last time point of observation without signs of tolerance. No

remarkable effect induced by bortezomib or CR4056, alone or in co-treatment, was observed on body weight changes.

Conclusions: The present study evidences a significant and long lasting analgesic effect of CR4056, which could represent a new therapeutic option for the treatment of bortezomib-induced chronic neuropathic pain.