Novel first-in-class sigma-1 antagonist shows encouraging efficacy profile in treatment of chemotherapy-induced peripheral neuropathy, neuropathic and post-operative pain

- First presentation of Phase II clinical studies with MR309 at the 16th World Congress on Pain demonstrate significant clinical benefits of a new analgesic in the treatment of patients with peripheral neuropathy of different aetiologies
- Potent and highly selective sigma-1 antagonist may provide a new way to approach the management of chemotherapy-induced neuropathy and neuropathic pain
- With neuropathic pain one of the most challenging pain conditions to manage, the clinical development of novel first-in-class sigma-1 antagonist reflects Mundipharma's commitment to bring innovative new treatments to patients suffering from pain

Cambridge, UK, 29 September 2016 – New Phase II data presented for the first time at the 16th World Congress on Pain have demonstrated that the novel first-in-class sigma-1 antagonist MR309 has a promising efficacy profile in the treatment of different types of peripheral neuropathy. In one study, in patients with colorectal cancer treated with the standard oxaliplatin-based treatment regimens, the proportion of patients who developed neuropathy symptoms severe enough to limit self-care activities of daily living was only 3.0% in the MR309 group compared to 18.0% in the placebo group (p=0.046).[1]

Chemotherapy-induced peripheral neuropathy (CIPN) is the most prevalent complication of oxaliplatin and a commonly dose-limiting side effect which impairs functional capacity and reduces quality of life.[2,3,4,5] Neuroprotective therapies against CIPN have been tested but, up until now, none have demonstrated unequivocal efficacy.[6,7] This is the first report of the efficacy of an agent that specifically targets the putative pathophysiological mechanisms involved in neurotoxicity and neuropathic pain, and represents real progress and innovation in the field of analgesic drug development.[1]

"The management of chemotherapy-induced peripheral neuropathy is severely hindered by the current lack of effective treatments," said Dr Harry Smith, Head of Medical Affairs for Pain, Mundipharma International. The results of this Phase II study suggest MR309 could be used as an adjunctive treatment in the management of oxaliplatin-based chemotherapy regimens. By reducing the risk of these patients developing severe neuropathy symptoms, MR309 could result in a significant reduction in the numbers of patients who have to discontinue oxaliplatin," he added.

In a second study, in patients with chronic post-surgical neuropathic pain, repeated doses of MR309 achieved clinically significant pain relief.[8] MR309 was associated with statistically significant reductions in 24-hour average pain intensity and 'worst pain' over days 15-28 compared with placebo.[8] The percentage of patients requiring rescue medication was higher in the placebo group than the MR309 group at all on-treatment study visits, as well as the off-treatment visit at day 35.[8] Results for all other visual analogue scale- and questionnaire-based efficacy endpoints generally showed greater pain reductions in favour of the MR309 group compared with placebo.[8]

Planned analysis by surgery location showed that a better response to MR309 was observed in patients with non-spinal surgery pain, which is probably because spinal surgery pain is often a mixed (and not solely neuropathic) pain.[8]

Neuropathic pain is a clinical manifestation characterised by spontaneous ongoing or shooting pains and evoked amplified pain responses after noxious or non-noxious stimuli.[9] Often accompanied by mood, sleep and cognitive complications, neuropathic pain can significantly interfere with patients' quality of life.[10] Current therapies for neuropathic pain are not satisfactory, which is why new drugs acting on novel molecular targets are being investigated.[9]

"Mundipharma is committed to developing new treatments to help patients better manage their pain," continued Dr Smith. New studies are planned to further investigate MR309 in the setting of chemotherapy-induced peripheral neuropathy, and to support the further development of this novel drug for the treatment of post-surgical neuropathic pain," Dr Smith added.

Efficacy in acute post-operative pain

MR309 is also being investigated as a treatment of acute post-operative pain. Effective control of post-operative pain is essential for the care of surgical patients, and to reduce the risk of postoperative complications.[11]

Post-operative pain is commonly managed with opioids, which are often administered intravenously using a patient-controlled analgesia (PCA) system that enables continuous dose adjustment according to individual patients' needs. However, opioid analgesics are typically associated with a number of side effects, including sedation, dizziness, nausea, vomiting, constipation, tolerance, and respiratory depression.[12] Because neuropathic and inflammatory mechanisms are also known to be involved in post-operative pain, the addition of other types of analgesic has become well established in this setting.[13]

Earlier pre-clinical studies with MR309 had demonstrated that, following systemic administration, this novel sigma-1 antagonist was effective in potentiating opioid analgesia without inducing the undesirable phenomena commonly associated with opioid use, such as tolerance and an abnormally heightened sensitivity to pain.[14]

Results of an exploratory Phase II study in patients undergoing elective non-malignant hysterectomy, presented for the first time at the 16th World Congress on Pain, showed that the analgesic effects of the study medication (MR309 or placebo) were obtained with a similar total amount of self-administered and rescue morphine in both treatment groups. In other words, there was no difference in the total amount of morphine administered to either treatment group.[15]

MR309 administration to patients before surgery resulted in differences in:

- the need for concomitant antiemetic medication[15]
- reduction in acute opioid-associated adverse events[15]
- reduction in pain intensity for up to 24 hours post-surgery[15]
- pain intensity in patients who did not self-administer morphine (as PCA) within 30 minutes post-surgery[15]

“Based on these exploratory Phase II data, further properly powered studies will be undertaken to investigate the effects of sigma-1 antagonists for the treatment of acute post-operative pain,” Dr Smith concluded.

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Notes to editors:

About MR309

MR309 (E-52862) was discovered by Laboratorios del Dr. Esteve, S.A.U. (ESTEVE), a leading Spanish pharmaceutical chemical group with expertise in early research and drug discovery in pain. Mundipharma licenced in the full global rights for MR309 in May 2016 and is responsible for the full development, licencing and commercialisation of the drug globally.

About Mundipharma

Mundipharma and its network of independent associated companies are privately owned companies and joint ventures covering the world's pharmaceutical markets. These companies are committed to bringing to patients the benefits of significant new treatment options in the core therapy areas of pain, respiratory, addiction, oncology and inflammatory conditions. Through innovation, design and acquisition, Mundipharma delivers important treatments to meet the most pressing needs of patients, healthcare professionals and health systems worldwide. For further

information, please visit: www.mundipharma.com

About ESTEVE

ESTEVE is a leading pharmaceutical chemical group based in Barcelona, Spain. Since it was founded in 1929, ESTEVE has been firmly committed to excellence in healthcare, dedicating efforts to innovative R&D of new medicines for unmet medical needs and focusing on high science and evidence-based research. ESTEVE has a strong partnership approach to drug discovery, development and commercialisation. The company works both independently and in collaboration to bring new, differentiated best-in-class treatments to patients who need them. The company currently employs 2,300 professionals and has subsidiaries and production facilities in several European countries, USA, China and Mexico. More about ESTEVE at www.esteve.com and www.esteve.com/research-development

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