# CEBRANOPADOL, A NOVEL FIRST-IN-CLASS ANALGESIC: EFFICACY, SAFETY, TOLERABILITY IN PATIENTS WITH PAIN DUE TO DIABETIC PERIPHERAL NEUROPATHY (DPN)

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## INTRODUCTION

With 382 million people diagnosed with diabetes mellitus worldwide in 2013 and a global prevalence of 8.3%, diabetes mellitus has become a global burden[1]. Clinical and subclinical neuropathy has been estimated to occur in 10% to 100% of diabetic patients, depending upon the diagnostic criteria and patient populations examined. Prevalence is a function of disease duration, and a reasonable figure, based upon several large studies, is that approximately 50% of patients with diabetes will eventually develop neuropathy[2]. A third of patients with diabetic polyneuropathy develop painful DPN which has a negative impact on physical and mental Quality of Life compared with painless diabetic neuropathy[3].

Cebranopadol is a novel first-in-class analgesic. It acts as a nociceptin/orphanin FQ peptide (NOP) and opioid peptide (OP) receptor agonist and is currently in development for the treatment of chronic pain conditions. NOP and classical opioid receptor agonistic components of cebranopadol interacted synergistically to produce antihypersensitive effects in an animal model of neuropathic pain. We explored the effects of cebranopadol in a Phase 2 trial in subjects suffering from chronic pain due DPN.

## OBJECTIVES

To assess the analgesic efficacy, safety, and tolerability of once daily (QD) orally administered cebranopadol in a total of 3 fixed doses (100 µg, 300 µg, and 600 µg) compared to placebo in subjects with moderate to severe chronic pain due to DPN.

## METHODS

### GENERAL CHARACTERISTICS OF THE TRIAL POPULATION

Male or female subjects aged 18-80 years with well-controlled and stable type 1 or type 2 diabetes mellitus and a clinical diagnosis of painful DPN requiring analgesia for at least 3 months. An overall baseline pain intensity score ≥5 on the 11-point numerical rating scale (NRS) without intake of any analgesic was required. Other analgesics or concomitant treatment that could interfere with efficacy assessment of the investigational medicinal products (IMP) and/or safety of the subjects were either forbidden during the treatment phase of the trial or were to be given at stable dose.

### TRIAL DESIGN

Randomized, multi-site, double-blind, double-dummy, placebo- and active-controlled, parallel-group, dose-ranging trial.

Rescue medication for unacceptable pain due to DPN: acetaminophen (500 mg tablets) up to a maximum total daily dose of 2000 mg and on no more than 3 consecutive days.

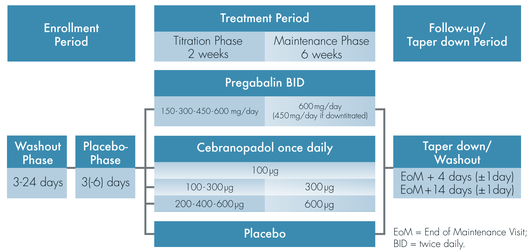
### EFFICACY EVALUATIONS

Change from baseline pain to the average 24-hour pain during Week 6 of the Maintenance Phase. The 24-hour pain was assessed once daily using an 11-point NRS and a 24-hour recall period.

### SAFETY EVALUATIONS

Adverse events, concomitant medication, vital signs, clinical laboratory, and electrocardiograms (ECG).

**Figure 1:** Flow diagram and trial treatments




EoM = End of Maintenance Visit; BID = twice daily.

### STATISTICAL ANALYSES

- The primary endpoint was analyzed by means of a mixed-effects model for repeated measures (MMRM). The model included fixed effects of pooled sites, treatment, time, treatment-by-time interaction, baseline and a subject-specific random effect. The primary analysis consisted of the contrasts of the individual cebranopadol doses versus placebo during Week 6 of the Maintenance Phase. The analysis of safety and tolerability parameters was descriptive.
- Pregabalin was included as an active comparator to assess assay sensitivity and was taken at a maintenance dose of 300 mg twice daily (BID) with the option to permanently reduce to 225 mg BID if not tolerated.

## RESULTS

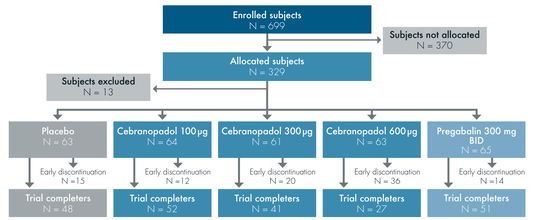
### SUBJECT DISPOSITION & BASELINE DEMOGRAPHICS

- A total of 82 active sites in 7 European countries and in the United States enrolled 699 subjects; 329 subjects were allocated to treatment (Figure 2).
- There were more men (61.7% to 79.0%) than women in every treatment arm. No relevant differences in demographic parameters were noted between treatment arms.
- Overall 316 subjects allocated to treatment were considered for the analysis; 314 subjects were assigned to the Safety Set and 312 subjects to the Full Analysis Set (FAS).

### EFFICACY

- Mean (standard deviation) baseline pain score was 6.84 (1.26) on the NRS (FAS). A clinically relevant difference of at least -0.7 points NRS compared to placebo for the change from baseline was shown with all cebranopadol doses with higher doses showing a larger difference. The difference to placebo was statistically significant for cebranopadol 600 µg QD (see Table 1).
- Although not formally tested, the results for pregabalin confirmed assay sensitivity of the trial and the clinical relevance of the results.
- A numerical separation between the active treatment arms and the placebo arm on the average 24-hour pain (MMRM) already occurred during the first 2 weeks of treatment (Figure 3).

**Figure 2:** Disposition of subjects (N) per treatment arm



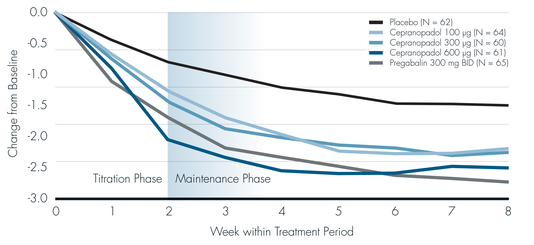

Two treatment arms (placebo and cebranopadol 600 µg) included 1 subject each that was allocated but not treated. Numbers of subjects allocated to the 5 treatment arms exclude 13 subjects that were excluded from the Safety Set and the FAS before unblinding.

**Table 1:** Change from baseline to the weekly average 24-hour pain during Week 6 of the Maintenance Phase – results of MMRM – Full Analysis Set

| | N | Estimate | Standard error | 95% Confidence interval | p-value |
|---|---|---|---|---|---|
| Placebo | 61 | -1.55 | 0.28 | (-2.10, -1.00) | |
| Cebranopadol 100 µg | 64 | -2.24 | 0.27 | (-2.78, -1.70) | |
| Cebranopadol 300 µg | 60 | -2.28 | 0.29 | (-2.86, -1.71) | |
| Cebranopadol 600 µg | 58 | -2.56 | 0.33 | (-3.20, -1.91) | |
| Pregabalin 300 mg BID | 64 | -2.79 | 0.27 | (-3.33, -2.26) | |
| Cebranopadol 100 µg - Placebo | | -0.70 | 0.37 | (-1.43, 0.04) | 0.0621 |
| Cebranopadol 300 µg - Placebo | | -0.74 | 0.39 | (-1.50, 0.02) | 0.0564 |
| Cebranopadol 600 µg - Placebo | | -1.01 | 0.41 | (-1.83, -0.20) | 0.0153 |

MMRM = Mixed-effects model for repeated measures;
N = number of subjects with at least 1 non-missing weekly change from baseline pain assessment.

**Figure 3:** Change from baseline to the weekly average 24-hour pain - results of MMRM - Full Analysis Set




### SAFETY/TOLERABILITY

- All doses of cebranopadol were safe without systematic effects on ECG, vital signs or laboratory parameters. The overall frequency of reported treatment emergent adverse events (TEAEs) was higher under cebranopadol treatment overall (80.2%) than under placebo treatment (69.4%). However, the overall frequency of reported TEAEs in the lowest cebranopadol 100 µg arm (73.4%) was similar to placebo and to pregabalin 300 mg BID treatment (75.4%). The overall frequency of reported TEAEs increased with dose and was higher in the cebranopadol 300 µg (82.0%) and 600 µg (85.5%) treatment arms (Table 2). Also the rate of early trial discontinuation increased with increasing dose of cebranopadol. The increase was primarily due to TEAEs occurring in the 14-day Titration Phase and may be a results of the forced titration employed in the trial.
- The most common TEAEs (≥10%) across all cebranopadol arms were nausea, dizziness, vomiting, fatigue, and somnolence (Table 2).
- Overall serious adverse events were low and occurred in 1, 2, and 4 subjects in the cebranopadol 100 µg, 300 µg, and 600 µg arms compared to 1 subject in the pregabalin 300 mg BID and 2 subjects in the placebo arm.

**Table 2:** Treatment emergent adverse events (occurring in at least 5% of subjects in at least 1 treatment arm) by Preferred Term – subject based analysis – Safety Set

| | | Cebranopadol | | | | |
|---|---|---|---|---|---|---|
| **Preferred Term** | **Placebo N (%)** | **100 µg N (%)** | **300 µg N (%)** | **600 µg N (%)** | **Overall N (%)** | **Pregabalin 300mg BID N (%)** |
| Total number of subjects | 62 (100.0) | 64 (100.0) | 61 (100.0) | 62 (100.0) | 187 (100.0) | 65 (100.0) |
| Subjects with TEAEs | 43 (69.4) | 47 (73.4) | 50 (82.0) | 53 (85.5) | 150 (80.2) | 49 (75.4) |
| Nausea | 6 (9.7) | 6 (9.4) | 22 (36.1) | 16 (25.8) | 44 (23.5) | 6 (9.2) |
| Dizziness | 6 (9.7) | 8 (12.5) | 10 (16.4) | 21 (33.9) | 39 (20.9) | 12 (18.5) |
| Vomiting | 2 (3.2) | 2 (3.1) | 10 (16.4) | 19 (30.6) | 31 (16.6) | 1 (1.5) |
| Fatigue | 2 (3.2) | 8 (12.5) | 11 (18.0) | 10 (16.1) | 29 (15.5) | 5 (7.7) |
| Somnolence | 1 (1.6) | 3 (4.7) | 8 (13.1) | 8 (12.9) | 19 (10.2) | 3 (4.6) |
| Hyperhidrosis | 2 (3.2) | 3 (4.7) | 8 (13.1) | 6 (9.7) | 17 (9.1) | 1 (1.5) |
| Constipation | 2 (3.2) | 3 (4.7) | 6 (9.8) | 7 (11.3) | 16 (8.6) | 6 (9.2) |
| Headache | 2 (3.2) | 3 (4.7) | 6 (9.8) | 3 (4.8) | 12 (6.4) | 4 (6.2) |
| Bacteriuria | 6 (9.7) | 5 (7.8) | 3 (4.9) | 3 (4.8) | 11 (5.9) | 6 (9.2) |
| Dry mouth | 1 (1.6) | 1 (1.6) | 1 (1.6) | 8 (12.9) | 10 (5.3) | 1 (1.5) |
| Oedema peripheral | 1 (1.6) | 3 (4.7) | 3 (4.9) | 1 (1.6) | 7 (3.7) | 6 (9.2) |
| Nasopharyngitis | 6 (9.7) | 3 (4.7) | 1 (1.6) | 1 (1.6) | 5 (2.7) | 5 (7.7) |
| Tremor | 0 | 1 (1.6) | 1 (1.6) | 1 (1.6) | 3 (1.6) | 4 (6.2) |
| Weight increased | 1 (1.6) | 0 | 0 | 0 | 0 | 5 (7.7) |

Sorted by cebranopadol overall. TEAE = treatment emergent adverse event; N = number of subjects; BID = twice daily.

## CONCLUSIONS

- In this exploratory trial in patients with moderate to severe chronic pain due to DPN, cebranopadol was effective, safe, and generally well-tolerated.
- A limitation of this trial was the forced up-titration design to target doses. The titration to individual best final dose of cebranopadol will require further optimization.

Clinical Trials.gov Identifier: NCT01939366, EudraCT Number: 2013-000473-68

### References

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