CEBRANOPADOL, A NOVEL FIRST-IN-CLASS ANALGESIC: EFFICACY, SAFETY, TOLERABILITY IN PATIENTS WITH MIXED CHRONIC LOW BACK PAIN

Annette Christoph, Clinical Development – Clinical Science, Grünenthal GmbH, Aachen, Germany · **Marie-Henriette Eerdekens,** Development, Grünenthal GmbH, Aachen, Germany · **Maurits Kok,** Clinical Development, Grünenthal GmbH, Aachen, Germany · **Gisela Volkers,** Data Sciences - Statistics, Grünenthal GmbH, Aachen, Germany · **Rainer Freynhagen,** Zentrum für Anästhesiologie, Intensivmedizin, Schmerztherapie und Palliativmedizin, Benedictus Krankenhaus Tutzing GmbH & Co. KG, Tutzing, Germany · **Presenting author: Dr. Annette Christoph,** annette.christoph@grunenthal.com

INTRODUCTION

Low back pain (LBP) is one of the most commonly reported chronic pain conditions worldwide causing activity limitation, work absence and an enormous economic burden[1].

Cebranopadol is a novel, highly potent analgesic acting as a nociceptin/orphanin FQ peptide (NOP) and opioid peptide (OP) receptor agonist with central analgesic activity. NOP and classical opioid receptor agonistic components of cebranopadol interacted synergistically to produce antihypersensitive effects in an animal model of neuropathic pain.

Cebranopadol is currently in clinical development for the treatment of chronic pain conditions.

This Phase 2 trial evaluated cebranopadol in subjects suffering from moderate to severe chronic LBP.

OBJECTIVES

To assess the analgesic efficacy, safety, and tolerability of once daily orally administered cebranopadol in a total of 3 fixed doses (i.e., 200 µg, 400 µg, and 600 µg cebranopadol) compared to placebo in subjects with moderate to severe chronic LBP.

METHODS

GENERAL CHARACTERISTICS OF THE TRIAL POPULATION

Male and female subjects aged 18 – 80 years with a clinical diagnosis of chronic LBP of non-malignant origin treated with either opioid or non-opioid analgesic medication for at least 3 months. An average 24-hour, analgesic medication free baseline pain score of ≥5 on the 11-point numerical rating scale (NRS) during the 3 days preceding randomization was required.

Other analgesics (e.g., opioids, NSAIDs, some anti-depressants) or concomitant treatments that could interfere with the efficacy assessment of the investigational medicinal product (IMP) and/or safety of the subjects were either forbidden during the Treatment Period of the trial or had to be given at a stable dose.

TRIAL DESIGN

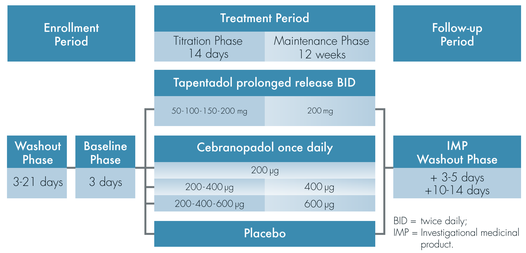
Randomized, multi-center, double-blind, double-dummy, placebo- and active–controlled, parallel-group, multiple oral dose trial.

Rescue medication: acetaminophen (500 mg tablets) up to a maximum total daily dose of 2000 mg.

EFFICACY EVALUATIONS

- Primary endpoint for the United States (US) region: Change from baseline pain to the average 24-hour pain during Week 12 of the Maintenance Phase.
  Subjects recorded their 24-hour pain daily on the NRS. Baseline pain was calculated as the average over the three 24-hour pain assessments of the baseline phase.
- Primary endpoint for the European Union (EU) and other non-US countries: Change from baseline pain to the weekly average 24-hour pain during the entire 12 weeks of the Maintenance Phase of the double-blind Treatment Period (not discussed in this poster).
- Responder rates (≥50% pain reduction) at Week 12 of the Maintenance Phase.

Figure 1: Flow diagram and trial treatments



SAFETY EVALUATIONS

Include adverse events, concomitant medication, vital signs, clinical laboratory, and electrocardiograms.

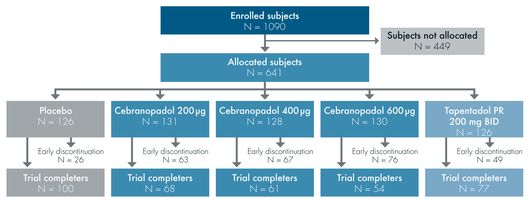
STATISTICAL ANALYSES

- The primary endpoint was analyzed by means of a mixed-effects model for repeated measures (MMRM) on the Full Analysis Set (FAS). The model included fixed effects of pooled sites (country), treatment, time, treatment-by-time interaction, baseline and a subject-specific random effect. To control the family-wise error rate, a gatekeeping and Hochberg multiple-comparison procedure was used. The primary analysis consisted of the contrasts of the individual cebranopadol doses versus placebo during Week 12 of the Maintenance Phase.
- Tapentadol prolonged release (PR), which has been proven to be an effective treatment in chronic LBP[2] was included as an active comparator to assess assay sensitivity and was taken at a maintenance dose of 200 mg twice daily (BID).

RESULTS

SUBJECT DISPOSITION AND BASELINE DEMOGRAPHICS

Figure 2: Disposition of subjects per treatment arm



Three treatment arms include subjects that were allocated to the arm but not treated (cebranopadol 200 µg and 400 µg: 1 subject each; cebranopadol 600 µg: 2 subjects).Two subjects were excluded from the Full Analysis Set due to lack of all pain assessments after first IMP intake.
N = number of subjects; BID = twice daily; PR = prolonged release.

- A total of 79 active trial sites in 11 European countries enrolled 1090 subjects; 641 subjects were randomly allocated to treatment.
- The FAS comprised a total of 223 men and 412 women. No other relevant differences in demographic parameters and baseline characteristics were noted between treatment arms.
- Mean (standard deviation) baseline pain intensity was 7.1 (1.17) on the NRS and was well balanced between all treatment arms.
- Subjects suffered from pain with and without a likelihood of a neuropathic pain component. At baseline, 33.5% of subjects were painDETECT positive, 29.1% painDETECT unclear, and 35.4% painDETECT negative; the distribution reflects published data[3].
- On average, 36.5% of subjects in the FAS had been pretreated with opioids, and 91.0% with non-opioids for their LBP.

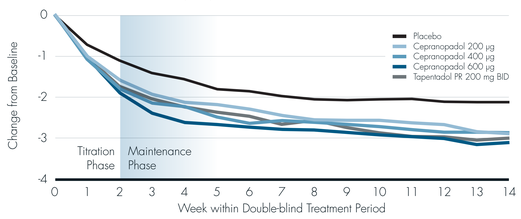
EFFICACY

Table 1: Change from baseline to the average 24-hour pain (NRS) during Week 12 of the Maintenance Phase - difference to Placebo (FAS) – results of MMRM

	N	Estimate	Standard error	95% Confidence interval	p-value
Placebo	125	-2.16	0.21	[-2.58, -1.74]	
Cebranopadol 200µg	122	-2.95	0.23	[-3.41, -2.50]	
Cebranopadol 400µg	120	-2.95	0.25	[-3.44, -2.47]	
Cebranopadol 600µg	117	-3.18	0.26	[-3.70, -2.66]	
Tapentadol PR 200 mg BID	123	-3.05	0.23	[-3.50, -2.60]	
Cebranopadol 200µg - Placebo		-0.79	0.30	[-1.39, -0.19]	0.0095
Cebranopadol 400µg - Placebo		-0.79	0.32	[-1.41, -0.17]	0.0122
Cebranopadol 600µg - Placebo		-1.02	0.33	[-1.67, -0.37]	0.0021

Trial week defined as a sequential 7-day interval subsequent to the Baseline Visit.
N = Number of subjects with at least 1 week with non-missing change from baseline pain assessment; BID = twice daily; PR = prolonged release; NRS = numeric rating scale; FAS = Full Analysis Set; MMRM = mixed-effects model for repeated measures.

Figure 3: Change from baseline to the weekly average 24-hour pain (NRS) - MMRM estimates (FAS)



- The primary endpoint for all 3 cebranopadol doses was statistically significantly different from placebo while preserving the family-wise error rate at an alpha level of 0.05 (Table 1).
- A numerical separation between the active treatment arms and the placebo arm on the weekly average 24-hour pain (MMRM) already occurred during the first 2 weeks of treatment (Figure 3).
- Although not formally tested, the result for tapentadol confirmed assay sensitivity of the trial and the clinical relevance of the results.
- In observed cases 36.5%, 40.6%, 38.9% of subjects on cebranopadol 200 µg, 400 µg, and 600 µg, respectively, 43.8% of subjects on tapentadol PR and 27.5% of placebo treated subjects reported ≥50% pain reduction at Week 12 of the Maintenance Phase compared to baseline.

SAFETY

- The use of cebranopadol 200 µg, 400 µg, and 600 µg for treatment in subjects with chronic LBP was safe without clinically relevant, systematic effects on vital signs, laboratory parameters and electrocardiograms.
- The most frequently reported treatment emergent adverse events (TEAEs) were dizziness, nausea, vomiting, constipation, fatigue, somnolence, headache, and hyperhidrosis (Table 2).
- Cebranopadol doses of 400 µg and 600 µg were less well tolerated than cebranopadol 200 µg and led to higher treatment discontinuation rates. This difference was primarily due to TEAEs occurring in the forced 2-week Titration Phase (discontinuation rates due to TEAEs: 13.0%, 21.9%, and 34.6% of subjects on cebranopadol 200 µg, 400 µg, and 600 µg arm, respectively). Consequently, further optimization of the titration scheme is warranted.

Table 2: Treatment emergent adverse events (TEAEs occurring in at least 5% of subjects for cebranopadol overall) by Preferred Term – subject based analysis – Safety Set

	Placebo	Cebranopadol				Tapentadol PR
Preferred Term	N (%)	200 µg N (%)	400 µg N (%)	600 µg N (%)	Overall N (%)	200mg BID N (%)
Total number of subjects	126 (100.0)	130 (100.0)	127 (100.0)	128 (100.0)	385 (100.0)	126 (100.0)
Subjects with TEAEs	82 (65.1)	108 (83.1)	107 (84.3)	115 (89.8)	330 (85.7)	100 (79.4)
Dizziness	11 (8.7)	34 (26.2)	42 (33.1)	62 (48.4)	138 (35.8)	36 (28.6)
Nausea	8 (6.3)	29 (22.3)	38 (29.9)	46 (35.9)	113 (29.4)	33 (26.2)
Somnolence	6 (4.8)	24 (18.5)	25 (19.7)	21 (16.4)	70 (18.2)	18 (14.3)
Vomiting	5 (4.0)	19 (14.6)	19 (15.0)	31 (24.2)	69 (17.9)	15 (11.9)
Constipation	5 (4.0)	18 (13.8)	21 (16.5)	23 (18.0)	62 (16.1)	22 (17.5)
Fatigue	3 (2.4)	13 (10.0)	21 (16.5)	21 (16.4)	55 (14.3)	18 (14.3)
Headache	11 (8.7)	14 (10.8)	15 (11.8)	11 (8.6)	40 (10.4)	10 (7.9)
Hyperhidrosis	2 (1.6)	11 (8.5)	17 (13.4)	10 (7.8)	38 (9.9)	12 (9.5)

Sorted by cebranopadol overall. N = Number of subjects; PR = prolonged release; BID = twice daily.

CONCLUSIONS

- In subjects with moderate to severe chronic LBP, cebranopadol was effective – with all doses showing statistically significant differences from placebo for the primary endpoint – and safe within the dose range tested.
- A limitation of this trial was the forced up-titration design to target doses. The titration to individual best dose of cebranopadol will require further optimization.

ClinicalTrials.gov Identifier: NCT01725087, EudraCT Number: 2012-001920-36

References

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