

# Efficacy evaluation of LEVADEX™ (previously MAPO004) in treating a broad spectrum of acute migraine attacks including patients using triptans and patients not using triptans

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## OBJECTIVES

To evaluate the efficacy and safety of LEVADEX™, a novel orally inhaled formulation of dihydroergotamine (DHE) in development, in the treatment of a broad spectrum of acute migraine attacks including migraine with moderate and severe pain, migraine with nausea and vomiting, migraine with and without aura, and migraine in patients currently using triptans and patients not using triptans.

## BACKGROUND

Migraine patient treatment needs often are unmet by available therapies, including triptans, due in part to the inability to completely relieve symptoms consistently across a broad spectrum of acute migraine attacks. Historically the 2 hr response rates in clinical trials tend to be inversely related to the severity of the headache treated [1]. 50-70% of migraine attacks are associated with nausea. 20-30% of migraineurs vomit [2,3]. Oral medications may not be appropriate for migraineurs with significant nausea and vomiting [4]. 20-30% of migraineurs experience aura [2,3]. There are several documented differences between patients suffering from migraine with aura and patients who have migraine without aura, including a higher incidence of strokes and cardiovascular events in patients suffering from migraine with aura [5]. The pathophysiology of migraine with aura may also be different from migraine without aura. Cortical Spreading Depression (CSD) is known to be an initial event associated with aura. Migraine without aura may or may not be associated with CSD.

LEVADEX is a self-administered, novel orally inhaled form of DHE in development, 1.0 mg nominal dose (approximately 0.5 mg systemic equivalent dose), with T<sub>max</sub> and AUC similar to IV infusion, but with markedly lower C<sub>max</sub>. In this study, results from a large Phase 3 study were analyzed to evaluate the efficacy and safety of LEVADEX in treating specific types of migraine discussed above.

Figure 1. LEVADEX, in the TEMPO® inhaler



## METHODS

This is a post hoc analysis of a randomized, double-blind, placebo-controlled, two-arm, multicenter study. All measures were done on a scale of 0 = none, 1 = mild, 2 = moderate and 3 = severe. Pain Relief (PR) was defined as a reduction of pain from 3 or 2 to a final score of 1 or 0. Pain Free (PF) was defined as a reduction of pain from 3 or 2 to a final score of 0. PR efficacy rates at 10, 30 and 60 minutes and 2 and 4 hours were calculated in the LEVADEX and placebo groups between migraine with moderate versus severe intensity at time of treatment. Efficacy rates including PR and PF at 2 hours were calculated in the LEVADEX and placebo groups and compared between migraine with nausea and without, migraine with vomiting and without, and migraine with aura and without. PR and PF efficacy rates at 2 hrs were also compared between patients using triptans at the time of entry and those who were not.

## RESULTS

903 patients were randomized, 811 patients experienced a qualifying migraine and 792 patients who treated a qualifying migraine were included in the primary analysis (MITT population).

Table 1. Demographics and baseline characteristics

DEMOGRAPHIC	PLACEBO	LEVADEX
Randomized	453	450
Had a Qualifying Migraine	404	407
MITT	397	395
Age, mean yrs (Min, Max)	40 (18, 65)	41 (18, 65)
Sex		
Female, n (%)	362 (91%)	363 (92%)
HIT-6 score at baseline		
Mean (Min, Max)	66 (48,78)	66 (50, 78)
< 60, n (%)	36 (9%)	41 (10%)
≥ 60, n (%)	357 (91%)	352 (90%)

• On average patients were severely disabled due to migraine at baseline (mean HIT-6 score of 66)

Table 2. Pain severity and presence of aura, nausea and vomiting at the time of headache treatment

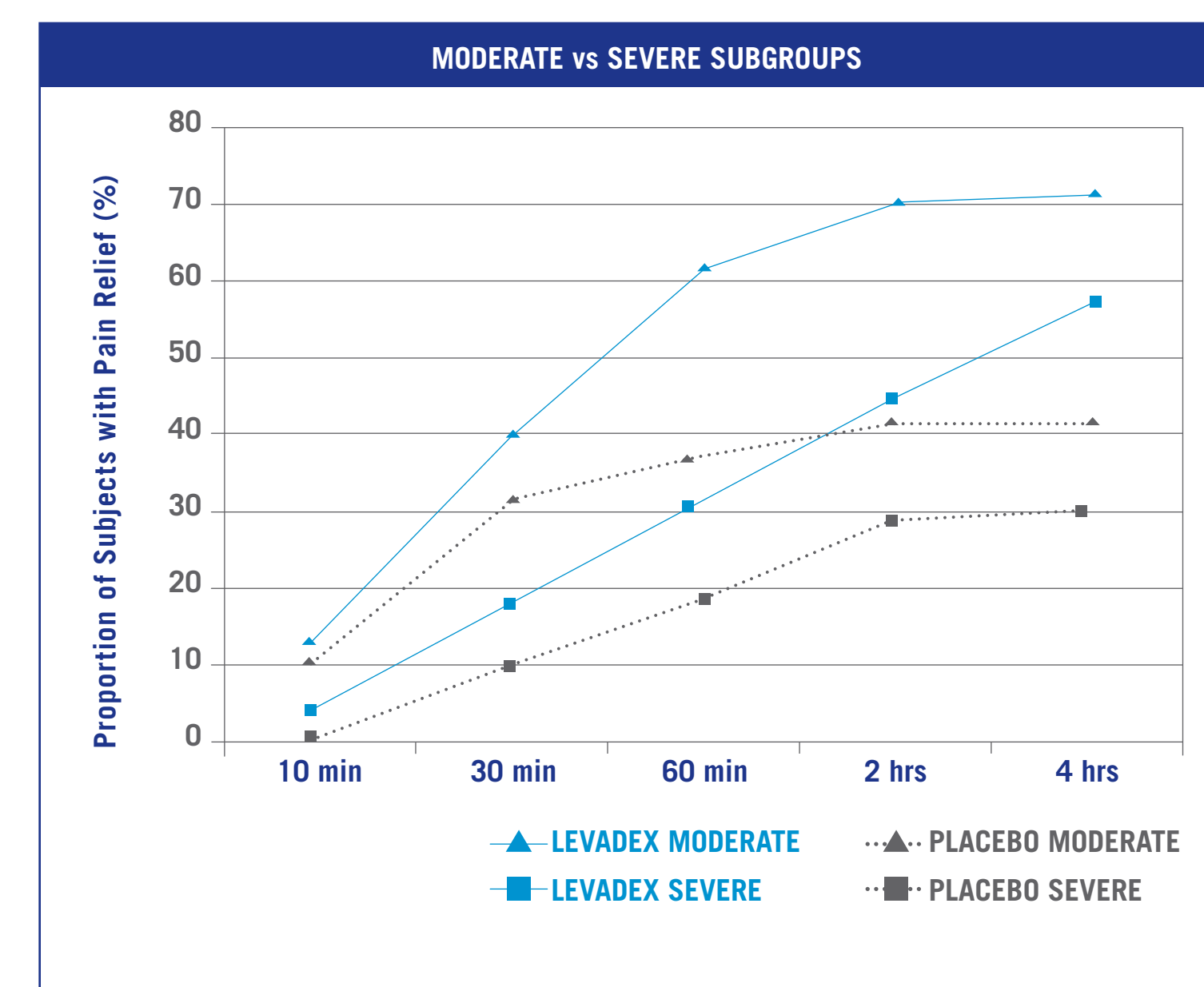
CHARACTERISTIC	PLACEBO	LEVADEX
Pain severity		
Moderate, n (%)	209 (53%)	217 (55%)
Severe, n (%)	188 (47%)	178 (45%)
Nausea		
With Nausea, n (%)	280 (71%)	269 (68%)
Without Nausea, n (%)	117 (29%)	124 (31%)
Vomiting		
With Vomiting, n (%)	27 (7%)	36 (9%)
Without Vomiting, n (%)	369 (93%)	356 (90%)
Aura		
With Aura, n (%)	140 (35%)	162 (42%)
Without Aura, n (%)	246 (62%)	221 (56%)

• The incidence of severe headaches treated was higher than in recently reported Phase 3 trials [6, 7]

## PAIN SEVERITY

The following post hoc analysis was performed to investigate the effectiveness of LEVADEX versus placebo in providing pain relief in patients with either moderate or severe pain at the time of treatment.

Figure 2. Efficacy of LEVADEX in treating migraine with moderate and severe pain at time of treatment

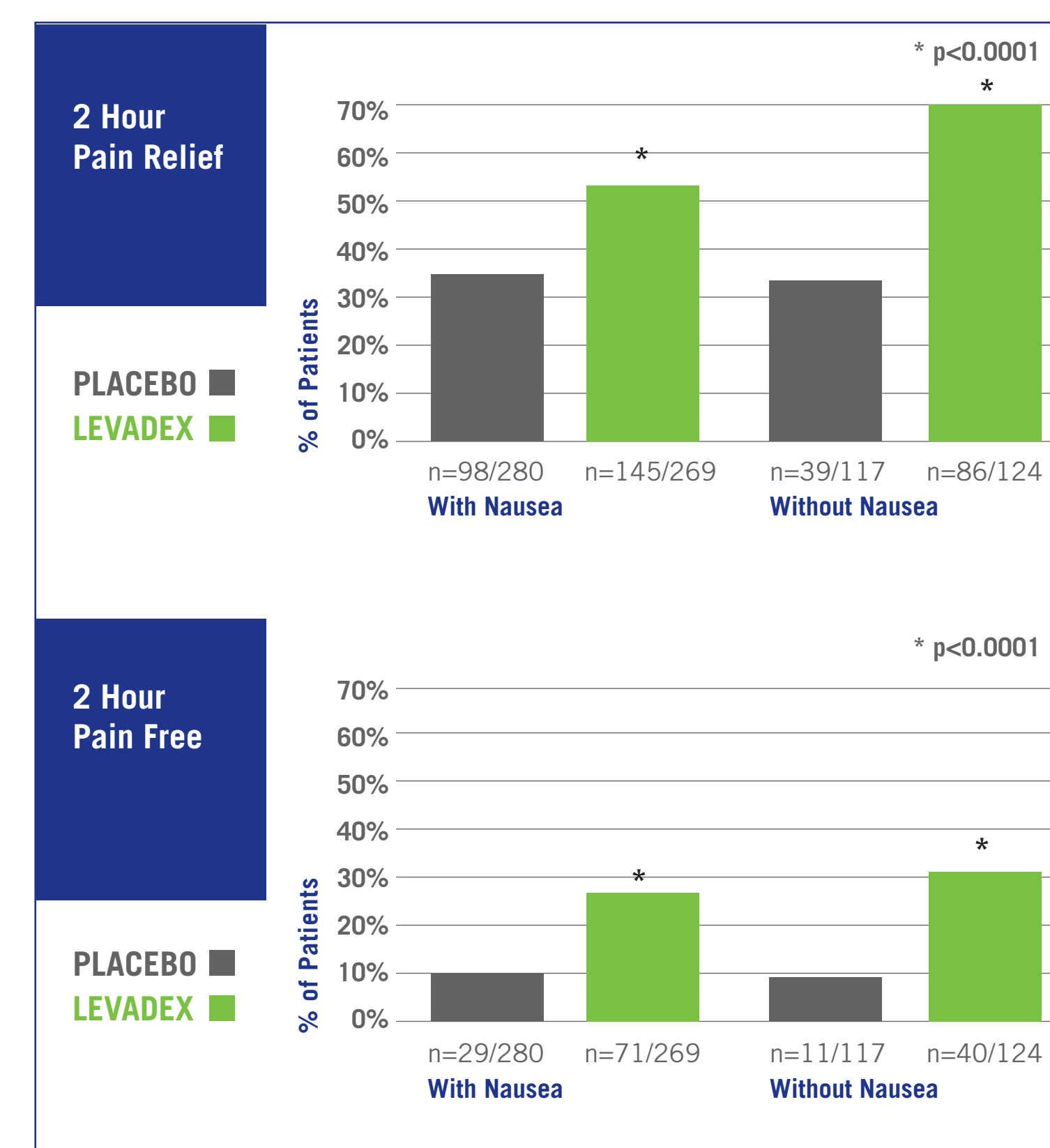


• 61% of moderate patients treated with LEVADEX had pain relief at 60 minutes compared to 37% with placebo (p<0.0001)  
 • 70% of moderate patients treated with LEVADEX had pain relief at 2 hours compared to 42% with placebo (p<0.0001)  
 • In the severe population, the pain relief response for LEVADEX was statistically significant compared to placebo at all time points starting at 10 minutes

## NAUSEA

The following post hoc analysis was performed to investigate the effectiveness of LEVADEX versus placebo in providing pain relief in patients with or without nausea at the time of treatment.

Figure 3. Efficacy of LEVADEX in treating migraine in patients with and without nausea at time of treatment



• LEVADEX was effective compared to placebo in patients with or without nausea

## VOMITING

The following post hoc analysis was performed to investigate the effectiveness of LEVADEX versus placebo in providing pain relief in patients with or without vomiting at the time of treatment.

Figure 4. Efficacy of LEVADEX in treating migraine in patients with and without vomiting at time of treatment



• LEVADEX was effective compared to placebo in patients with or without vomiting

## AURA

The following post hoc analysis was performed to investigate the effectiveness of LEVADEX versus placebo in providing pain relief in patients with or without aura at the time of treatment.

Figure 5. Efficacy of LEVADEX in treating migraine in patients with and without aura at time of treatment



• LEVADEX was effective compared to placebo in patients with or without aura

## TRIPATAN USE

The following post hoc analysis was performed to investigate the effectiveness of LEVADEX versus placebo in providing pain relief in patients who were currently using triptans at time of entry into the study and those who were not using triptans.

Figure 6. Efficacy of LEVADEX in treating migraine in patients currently using triptans and not using triptans



• LEVADEX was effective compared to placebo in patients currently using triptans and not using triptans

## CONCLUSIONS

These are post hoc analyses evaluating the efficacy of LEVADEX in treating a broad spectrum of migraine. P-values are not adjusted for multiplicity and refer to placebo versus LEVADEX comparisons in a demographic group. In this Phase 3 trial:

- LEVADEX was effective in treating a broad spectrum of migraine attacks
- LEVADEX was effective in treating migraine attacks with severe and moderate intensity of baseline pain
- In patients with severe intensity of pain, LEVADEX had statistically significant pain relief in 10 minutes
- LEVADEX was effective in treating migraine with and without nausea
- LEVADEX was effective in treating migraine with and without vomiting
- LEVADEX was effective in treating migraine with and without aura
- LEVADEX was effective in treating migraine in patients currently using triptans and those not using triptans

Based on these analyses, LEVADEX has potential to be effective in a broad spectrum of migraine. LEVADEX is continuing to be evaluated in a Phase 3 program.

## REFERENCE

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