

# Evaluation of Efficacy and Safety of LEVADEX™ in Treating Migraine with and without Allodynia and Reversing Allodynia, a Marker of Central Sensitization

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## OBJECTIVES

To evaluate the efficacy of LEVADEX™, a novel orally inhaled formulation of dihydroergotamine mesylate (DHE), in treating an acute attack of migraine accompanied by cutaneous allodynia compared to treating an attack without cutaneous allodynia. In addition, to evaluate the efficacy of LEVADEX in providing freedom from cutaneous allodynia, reversing established cutaneous allodynia, and blocking the development of cutaneous allodynia compared to placebo.

## BACKGROUND

Recent neuro-physiological studies have suggested that many migraine subjects develop central sensitization if their migraine attacks are severe in pain intensity or are of long duration [1,2,3]. The development of central sensitization often manifests clinically as cutaneous allodynia of the face and scalp, hereby referred to as allodynia [1]. Although precise measurement of allodynia requires extensive sensory testing involving sophisticated equipment, simple questionnaires have been developed to clinically assess the presence or absence of allodynia with a fair degree of reliability [4]. Recent epidemiological studies have also suggested that Medication Overuse Headache (MOH) mechanisms may also be related to central sensitization [5].

Several studies have suggested that triptans, the most commonly used acute migraine medications, fail to provide complete pain relief in subjects who demonstrate allodynia at the time of treatment [1,2,3]. In experimental models using electrophysiological recordings from the central trigeminal neurons, sumatriptan did not reverse central sensitization once established [6]. The presence of central sensitization might also explain why triptans have decreased efficacy in treating a migraine if used late in the course of that attack [7]. The decreased effectiveness of triptans in treating morning migraines may also be explained on this basis.

## BACKGROUND Cont.

Unlike the triptans, DHE has been shown to reverse central sensitization in animal models [6]. LEVADEX is a novel, self-administered, orally inhaled form of DHE in Phase 3 clinical development. LEVADEX delivers a 0.6 mg emitted dose (1.0 mg nominal dose), with T<sub>max</sub> and AUC similar to IV infusion, but with markedly lower C<sub>max</sub>. In this post hoc analysis, the effectiveness of LEVADEX in treating migraine pain with and without allodynia, in providing allodynia freedom, in reversing allodynia, and in blocking the development of allodynia were evaluated.

## METHODS

This is a post hoc analysis of a randomized, double-blind, placebo-controlled, two-arm, Phase 3 multicenter study. The presence or absence of allodynia at the time of drug administration was determined by a questionnaire (Figure 1). The questionnaire was administered at the time of treatment and at 2 hours post-dose. The distinction between established and developing allodynia was based on the progression of allodynia over 2 hours. Pain relief at 2 hours, pain free at 2 hours, sustained pain relief from 2 to 24 hours and sustained pain free from 2 to 24 hours measures were compared between the allodynic and non-allodynic subjects.

Figure 1. Allodynia questionnaire

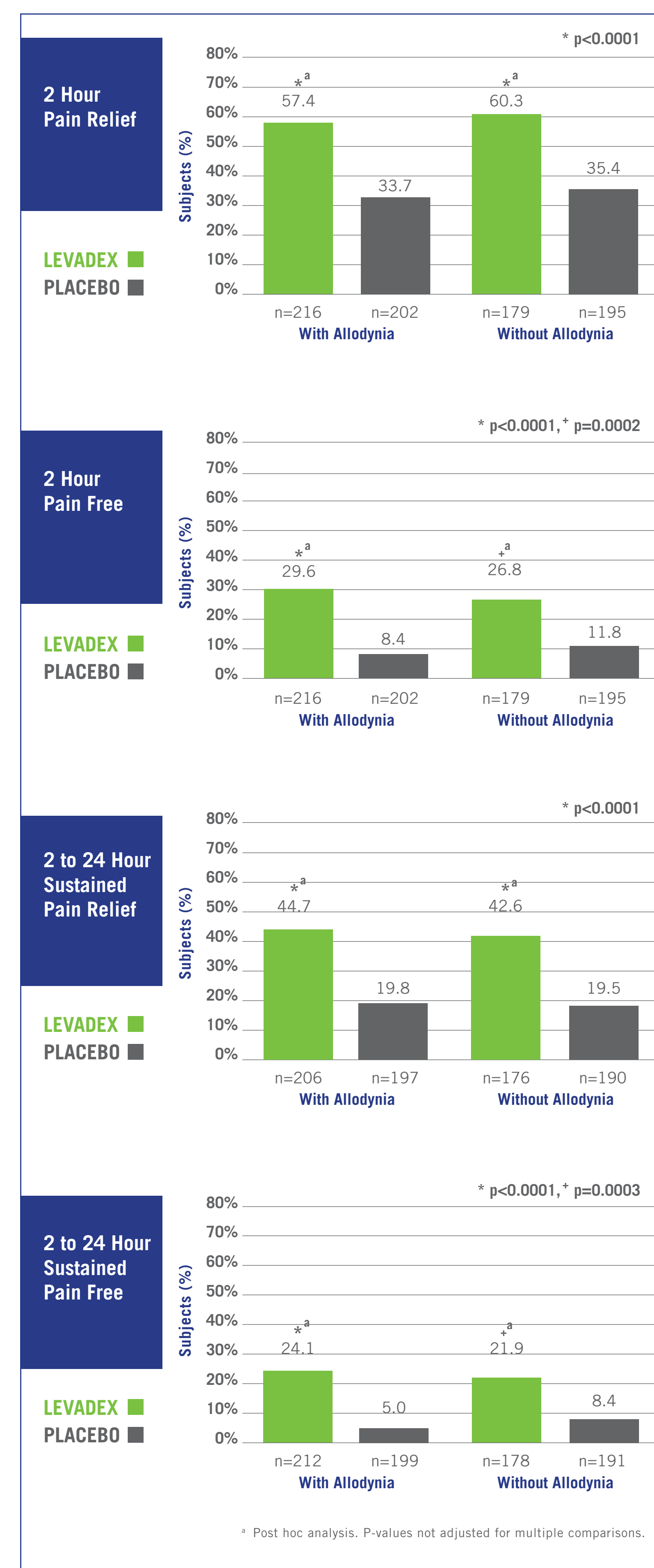
The presence of allodynia at the time of treatment was defined as answering "Yes" to at least two of the following questions:

1. Is your scalp tender to touch?
2. Does combing your hair bother you?
3. Does wearing your glasses or sunglasses bother you?
4. Does washing your face bother you?
5. Are your teeth and gums tender to touch?
6. Is your skin over the face tender to touch?

## RESULTS

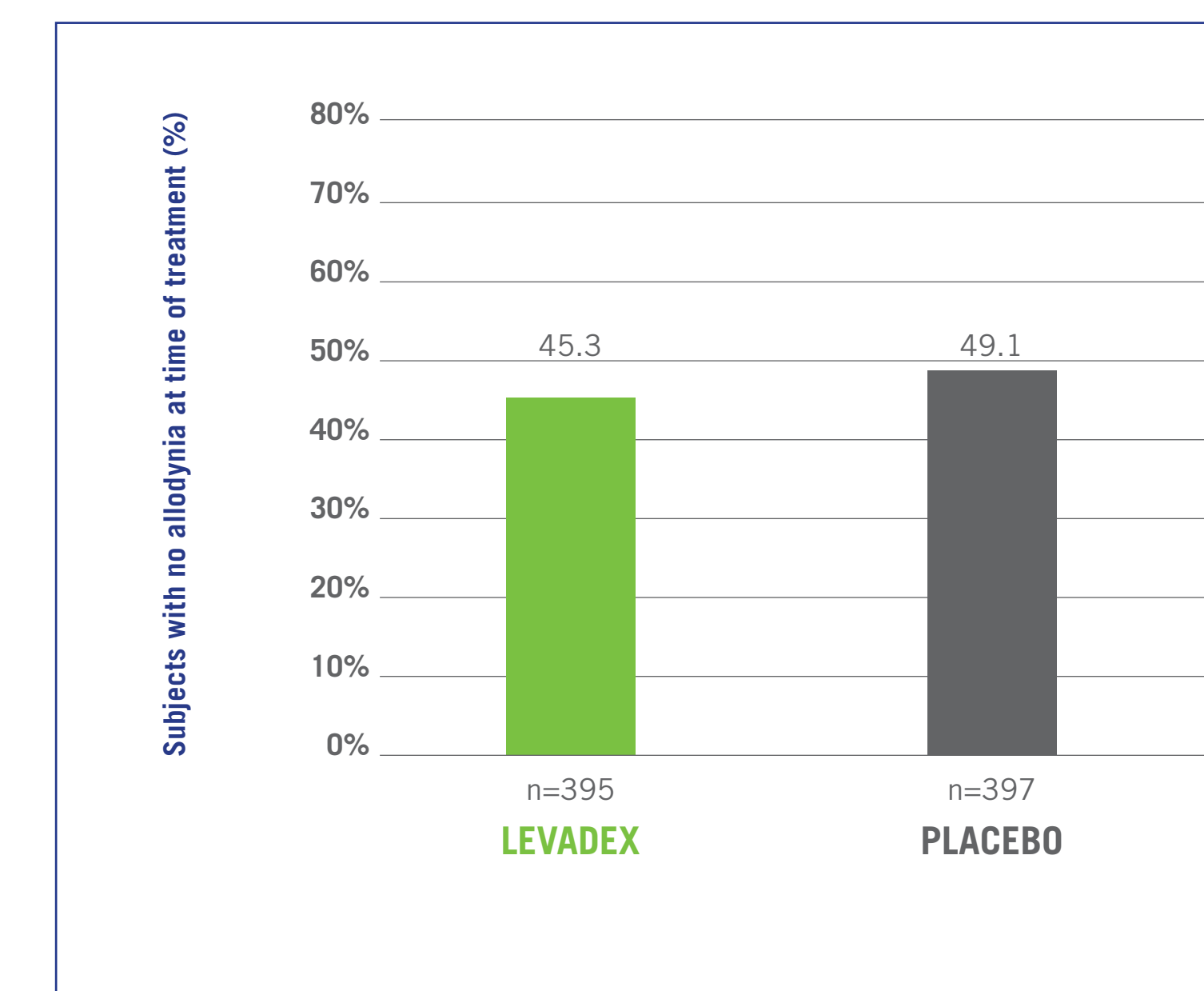
903 subjects were randomized and 811 subjects experienced a qualifying migraine. 792 subjects were included in the pre-specified mITT population for efficacy analysis.

Figure 2. Efficacy of LEVADEX in treating migraine pain with allodynia at time of treatment



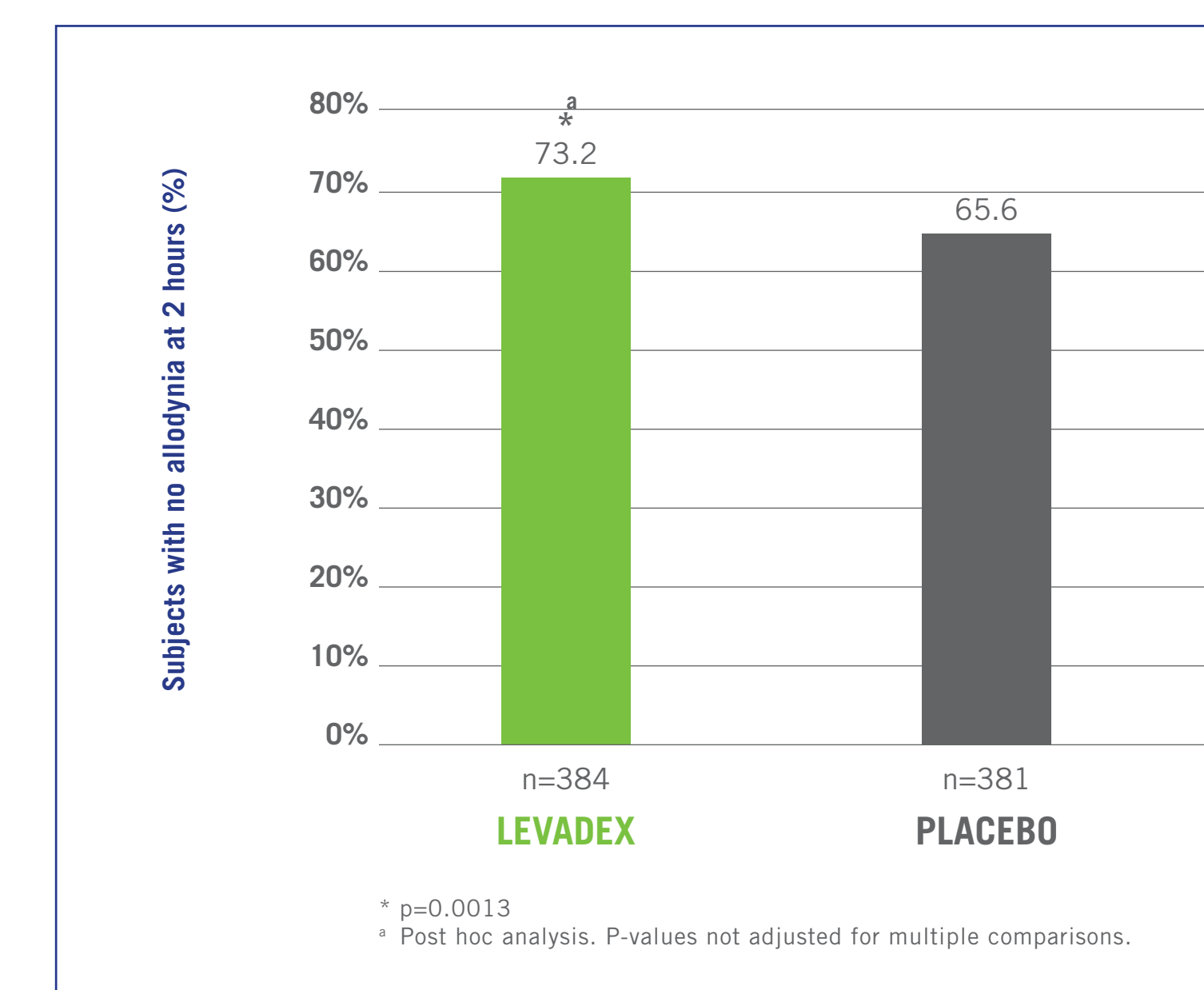
- LEVADEX was effective in providing pain relief and pain free at 2 hours and sustained pain relief and sustained pain free from 2 to 24 hours compared to placebo in subjects with and without allodynia at time of treatment.
- LEVADEX was equally effective in treating migraine with or without allodynia. There was no significant difference in pain relief and pain free efficacy measures in LEVADEX-treated migraines regardless of the presence or absence of allodynia at time of treatment.

Figure 3. Allodynia free at the time of treatment (baseline)



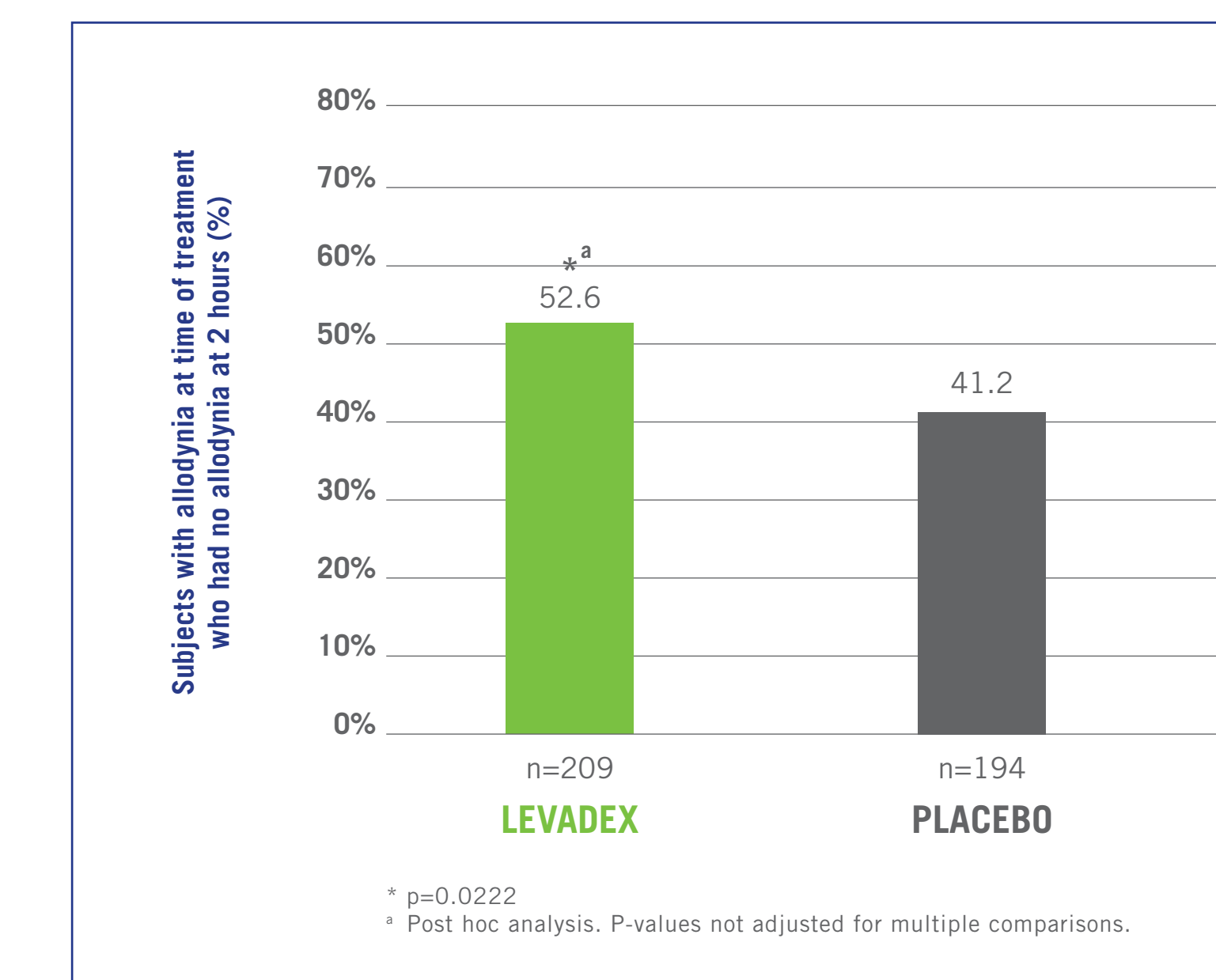
- At the time of treatment, allodynia free rates were similar between the LEVADEX and placebo groups.
- 45% of subjects on LEVADEX and 49% of subjects on placebo were allodynia free at time of treatment.

Figure 4. Allodynia free at 2 hours



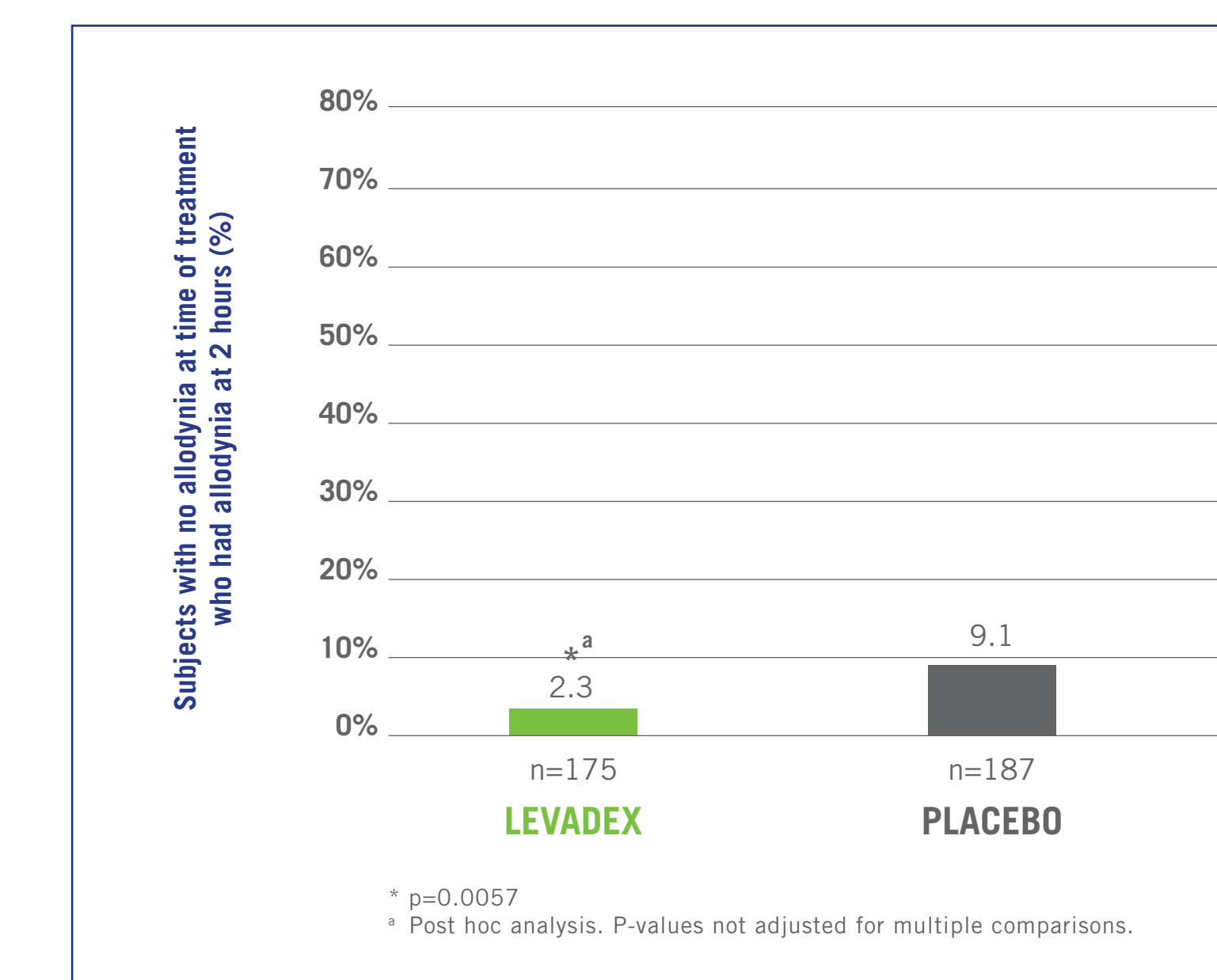
- LEVADEX more effectively provided allodynia free results at 2 hours after treatment compared to placebo.

Figure 5. Elimination of allodynia between time of treatment and 2 hours after treatment



- In those subjects with allodynia at the time of treatment, LEVADEX was more effective at eliminating allodynia at 2 hours after treatment compared to placebo.

Figure 6. Development of allodynia between time of treatment and 2 hours after treatment



- Of those subjects without allodynia at the time of treatment, only 2% of those on LEVADEX and 9% of those on placebo developed allodynia 2 hours later, suggesting that most subjects who would develop allodynia had developed it prior to drug administration.
- Of those subjects without allodynia at the time of treatment, LEVADEX prevented the development of allodynia at 2 hours after treatment more effectively than placebo.

## CONCLUSION

This evaluation was composed of post hoc analyses evaluating the efficacy of LEVADEX in treating migraine with and without allodynia. All statistical p-values are not adjusted for multiple comparisons. In this Phase 3 trial:

- LEVADEX was more effective in providing pain relief at 2 hours, pain free at 2 hours, sustained pain relief from 2 to 24 hours, and sustained pain free from 2 to 24 hours compared to placebo in subjects with or without allodynia at time of treatment.
- LEVADEX was equally effective in treating migraine with or without allodynia. There was no significant difference in efficacy measures between LEVADEX-treated migraines regardless of the presence or absence of allodynia at time of treatment.
- LEVADEX provided allodynia free results at 2 hours after treatment more effectively compared to placebo (p=0.0013).
- In those subjects with allodynia at the time of treatment, LEVADEX was more effective at eliminating allodynia at 2 hours after treatment compared to placebo (p=0.0222).
- In those subjects without allodynia at the time of treatment, LEVADEX more effectively prevented the development of allodynia at 2 hours after treatment compared to placebo (p=0.0057).

Based on these analyses of treating allodynia as a marker of central sensitization, LEVADEX may have the potential to be effective in a broad spectrum of migraine, including migraine with and without allodynia, as well as migraine treated late in an attack after central sensitization has occurred. LEVADEX continues to be evaluated in a Phase 3 program.

## REFERENCES

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