

Utility of LEVADEX™ in Situations Where Early Intervention Paradigm is Impractical

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LEVADEX™ (MAP0004) Orally Inhaled DHE

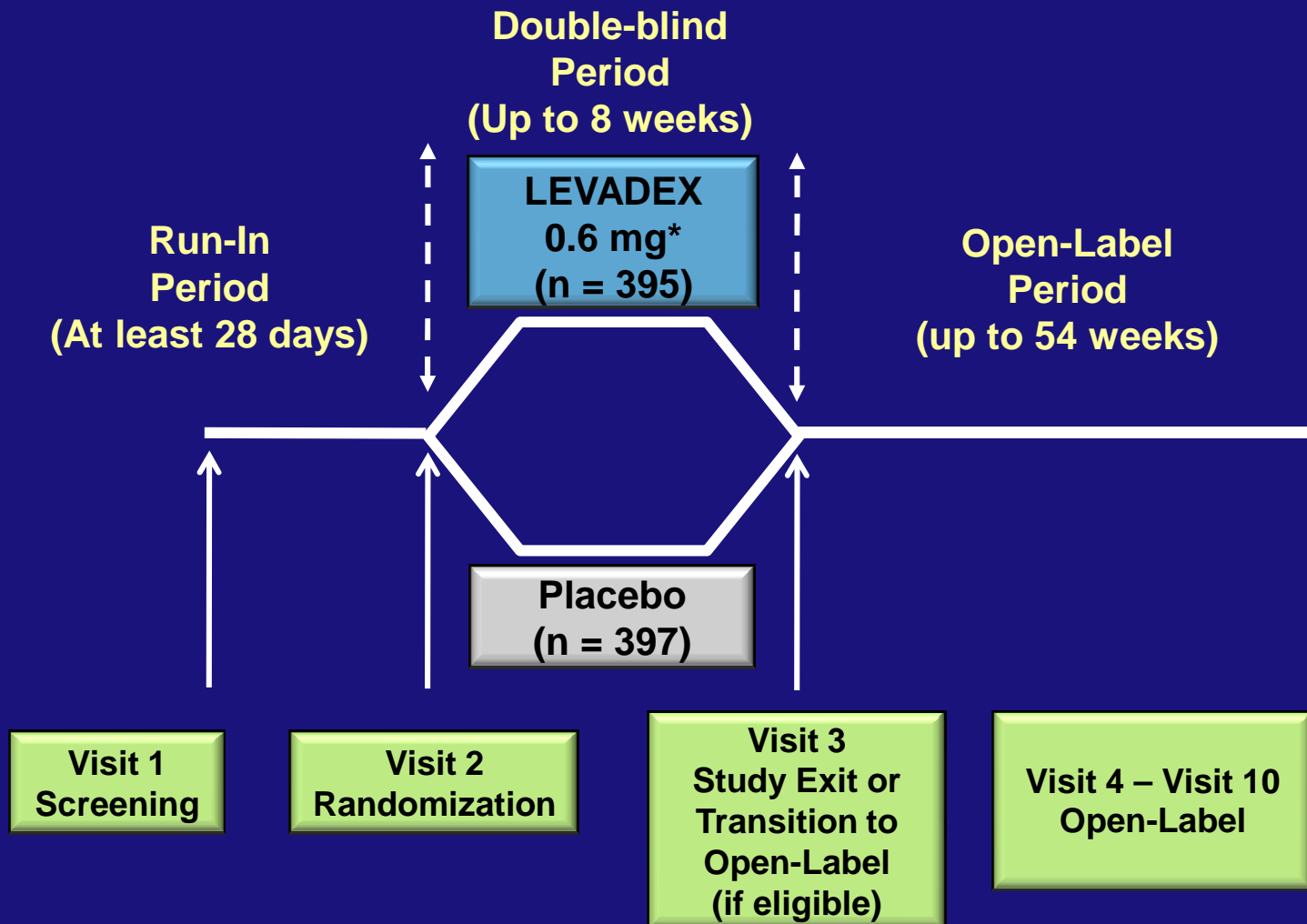
- DHE is a standard therapy for resistant migraine
- DHE has inconsistent absorption when administered through routes other than IV
- LEVADEX is a novel orally inhaled form of DHE in clinical development that has T_{max} similar to injection, but with lower C_{max} , and offers consistent absorption
- In a Phase 3 study, LEVADEX met all primary endpoints and provided both rapid and sustained pain relief in patients with migraine



Rationale for this Study

- **Early intervention is generally more effective**
- **However, many patients wait to take their medication**
 - **Want to be sure they have a migraine**
 - **Want to be sure they need a triptan**
 - **Hoarding of medicine for cost reasons**
 - **Do not want to take too strong a medicine if not needed**
- **DHE may reverse central sensitization, and therefore should work anytime, even when administered late**

LEVADEX™ (MAP0004) Phase 3 Clinical Study Design

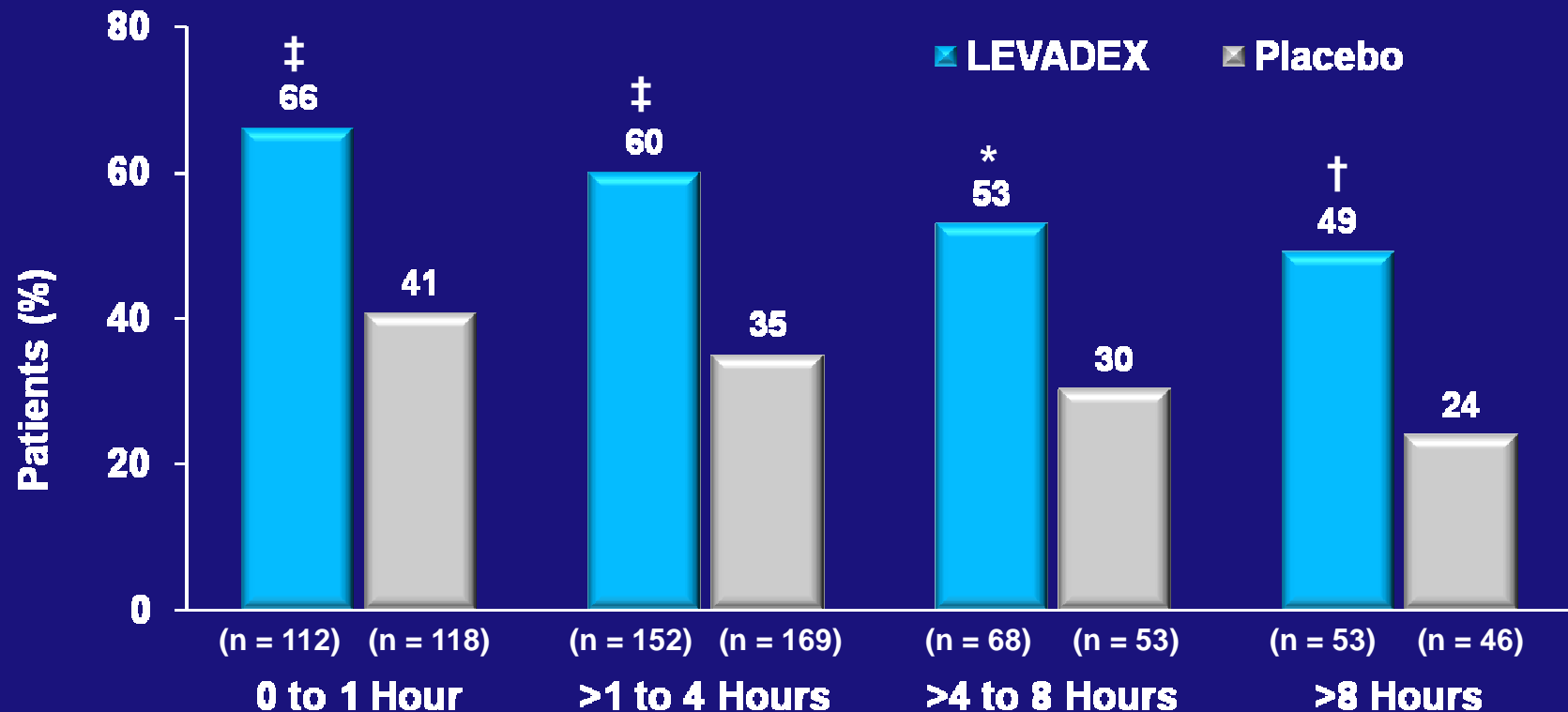


* 0.6 mg emitted dose (1.0 mg nominal dose)

Post Hoc Analysis of Time to Treatment in Phase 3 Study

- **903 patients randomized**
- **771 patients treated a moderate to severe qualifying migraine, recorded efficacy and time to treatment data, and were included in this post hoc analysis**
- **2 hr Pain Relief (PR) and 2 hr Pain Free (PF) rates were compared between active and placebo in those who treated their migraine within 1 hour, > 1 to 4 hrs, > 4 to 8 hrs, and > 8 hrs after the onset of headache**

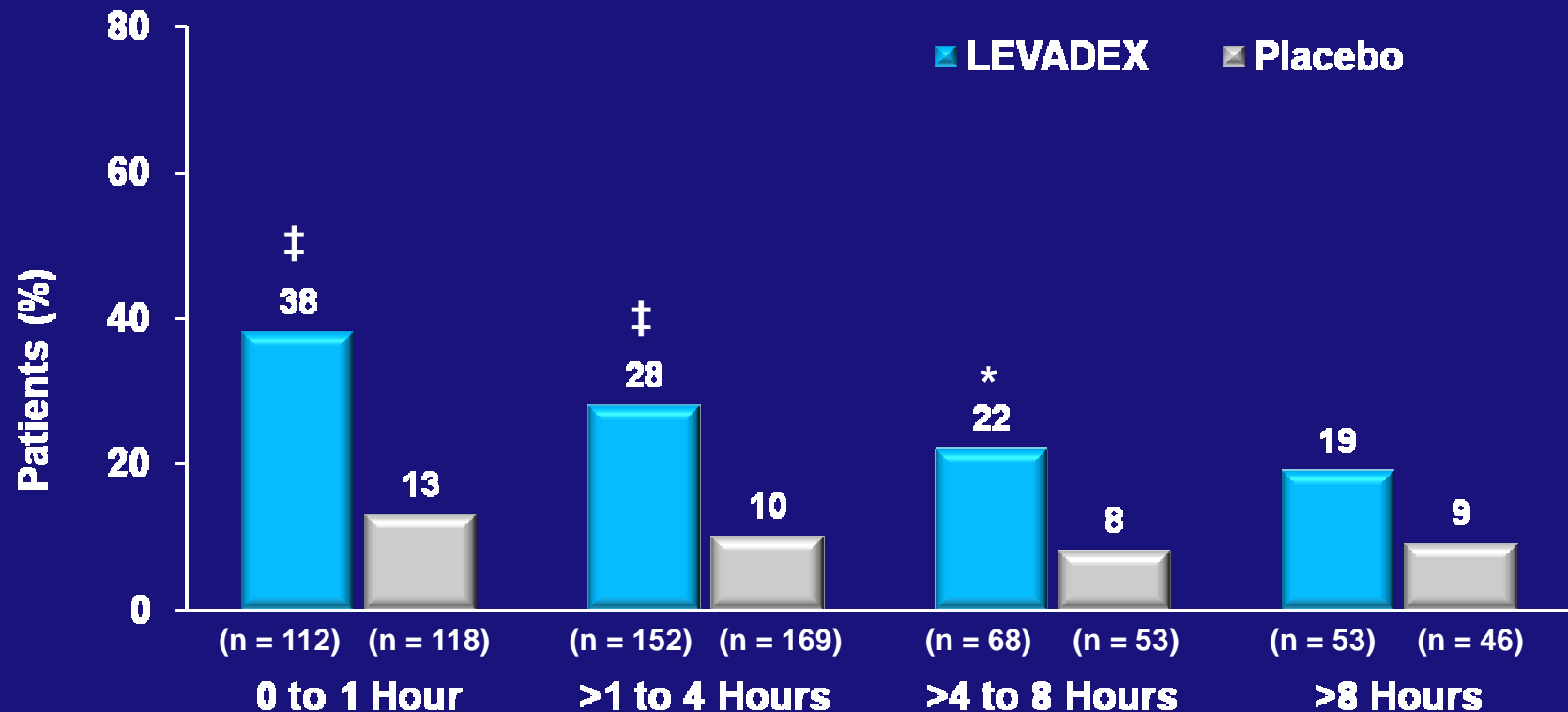
Pain Relief at 2 Hours as a Function of Time of Initiating Treatment after Start of Migraine



[‡] $P < 0.0001$; [†] $P < 0.01$; ^{*} $P < 0.05$ compared with placebo calculated using the Cochran-Mantel-Haenszel test controlling for baseline pain score; exploratory endpoints not adjusted for multiplicity.

Note: Post hoc analysis. P-values are not adjusted for multiple comparisons.

Pain Free at 2 Hours as a Function of Time of Initiating Treatment after Start of Migraine



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Note: Post hoc analysis. P-values are not adjusted for multiple comparisons.

LEVADEX was Well Tolerated

Adverse Events (Double-Blind Portion, Single Dose)

Adverse Events (AEs) in \geq 2% of Patients and > Placebo	Safety Population Patients (%)	
	LEVADEX (N = 404)	Placebo (N = 401)
Taste	6.4 %	1.7 %
Nausea	4.5 %	2.0 %
Cough	2.5 %	1.2 %
Vomiting	2.0 %	0.7 %

- In patients treated with LEVADEX, symptoms and sensitivities typically associated with triptans, such as chest discomfort and chest pain, were rare and occurred at similar rates compared with placebo
- No drug related serious adverse events were reported
- No clinically meaningful change in lung function in any treatment group in double-blind portion of study (single dose)

Discussion

- **Triptan efficacy is substantially reduced when administered late¹**
- **Potential explanation for decreased response when migraine is treated late is the development of central sensitization**
- **Animal models show that triptans may not reverse established central sensitization^{2,3}**
- **In the same animal model, DHE appears to reverse central sensitization³**

¹Aurora S, Barrodale P. *Headache*. 2009;49: 1001-1004.

²Burstein R, Jakubowski M. *Ann Neurol*. 2004;55:27-36.

³ Oshinsky ML. *Curr Pain Headache Rep*. 2006;10:225-30.

Conclusions

- **In this post hoc analysis of time to treatment in a Phase 3 study:**
 - **LEVADEX showed efficacy in treating a moderate or severe acute migraine attack even when it was administered as late as 8 hours after the start of a migraine**
 - **LEVADEX was well tolerated with few triptan-like sensations and no drug-related SAEs reported**
- **LEVADEX may help many migraineurs who are unable to treat their migraine early due to several practical real life situations**

Note: Post hoc analysis. P-values are not adjusted for multiple comparisons.

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