

Migraine Recurrence Rates: Case for Standardization of the Definition

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BACKGROUND

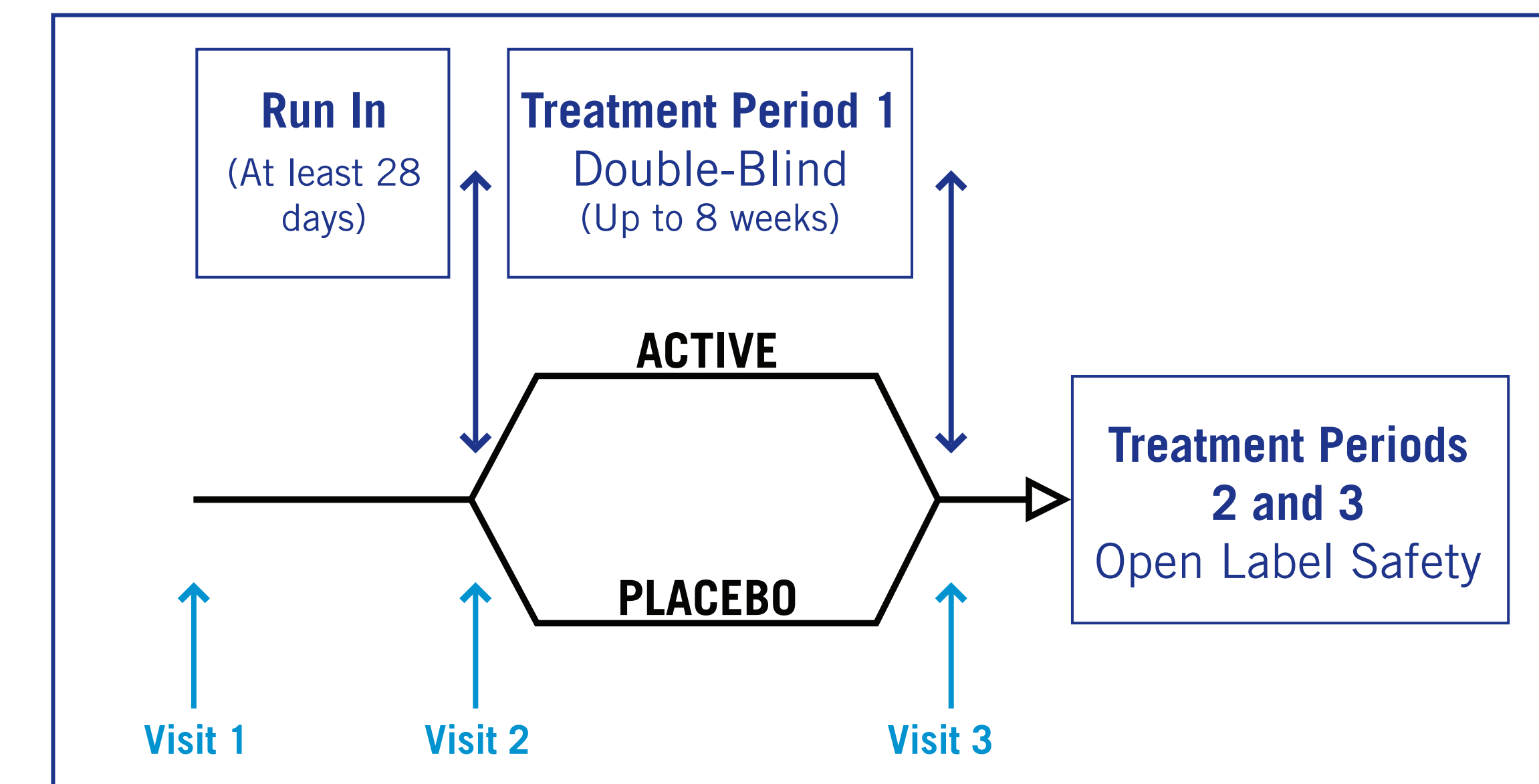
Several surveys have documented that rapid onset of action and prolonged pain relief are two key attributes of an effective acute migraine medication.[1,2] In clinical trials, measurement of time to onset of relief is well standardized. However, there is no standard for the measurement of prolonged relief. Physicians are familiar with and recognize the term “Recurrence” and often use it to assess the sustained action of a drug. However, there is no one accepted definition of recurrence, and many different methods are used to calculate recurrence rates. [3-5] As an alternative, Sustained Pain Relief (SPR) and Sustained Pain Free (SPF) data, defined as percentage of subjects who have Pain Relief/Free at 2 hours and sustain such relief through the next 22 hours, or 46 hours, without use of rescue medication, offer reasonable estimates of prolonged suppression of the attack. However, SPF and SPR with pain relief at 24 hours can be confused if not clearly presented. In this analysis different recurrence rates are calculated using different definitions from the literature to illustrate the unreliability of using this non-standardized end point for comparing different migraine treatments.

LEVADEX™ is a novel, orally inhaled formulation of dihydroergotamine (DHE) that was effective in the acute treatment of migraine in a Phase 3 trial.[6,7] DHE is generally considered to have a prolonged duration of action, which is considered significantly longer than triptans.[8] Recurrence data for LEVADEX was calculated using the different definitions and compared to the historical data for triptans obtained from the literature.

METHODS

This is a *post-hoc* analysis of a multicenter, double blind, Phase 3 study comparing LEVADEX 0.6 mg emitted dose (1.0 mg nominal) to placebo.

Figure 1. Clinical trial design



Four different definitions of recurrence were used:

Table 1. Recurrence definitions used in the analysis

Definition	Formula
A	$\frac{\text{\# of subjects with pain relief (PR) at 2 hrs, who had moderate or severe pain during next 22 or 46 hrs}}{\text{\# of subjects with PR at 2 hrs}}$
B	$\frac{\left[\begin{array}{l} \text{\# of subjects with PR at 2 hrs, who had moderate or severe pain during next 22 or 46 hrs} \\ + \\ \text{\# of subjects with PR at 2 hrs, who had mild or no pain during next 22 or 46 hrs but used rescue medication} \end{array} \right]}{\text{\# of subjects with PR at 2 hrs}}$
C	$\frac{\text{\# of subjects with PR at 2 hrs, who had moderate or severe pain during next 22 or 46 hrs}}{\text{\# of subjects in modified intent to treat (mITT) population}}$
D	$\frac{\left[\begin{array}{l} \text{\# of subjects with PR at 2 hrs, who had moderate or severe pain during next 22 or 46 hrs} \\ + \\ \text{\# of subjects with PR at 2 hrs, who had mild or no pain during next 22 or 46 hrs but used rescue medication} \end{array} \right]}{\text{\# of subjects in mITT population}}$

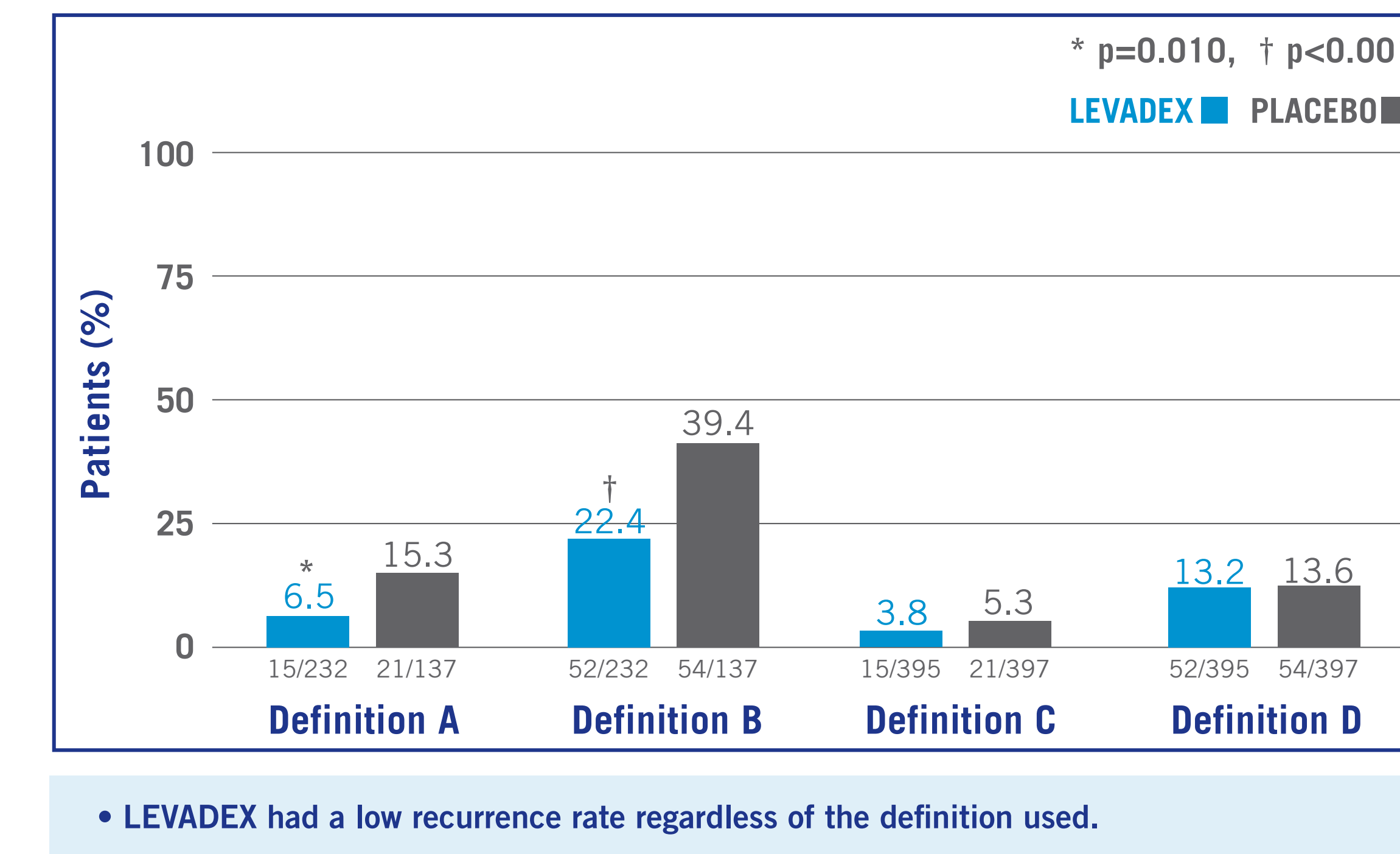
The rate of recurrence was also compared between different age groups (below 35 and above 35), and different severity of headache pain at the time of treatment (moderate vs severe).

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.

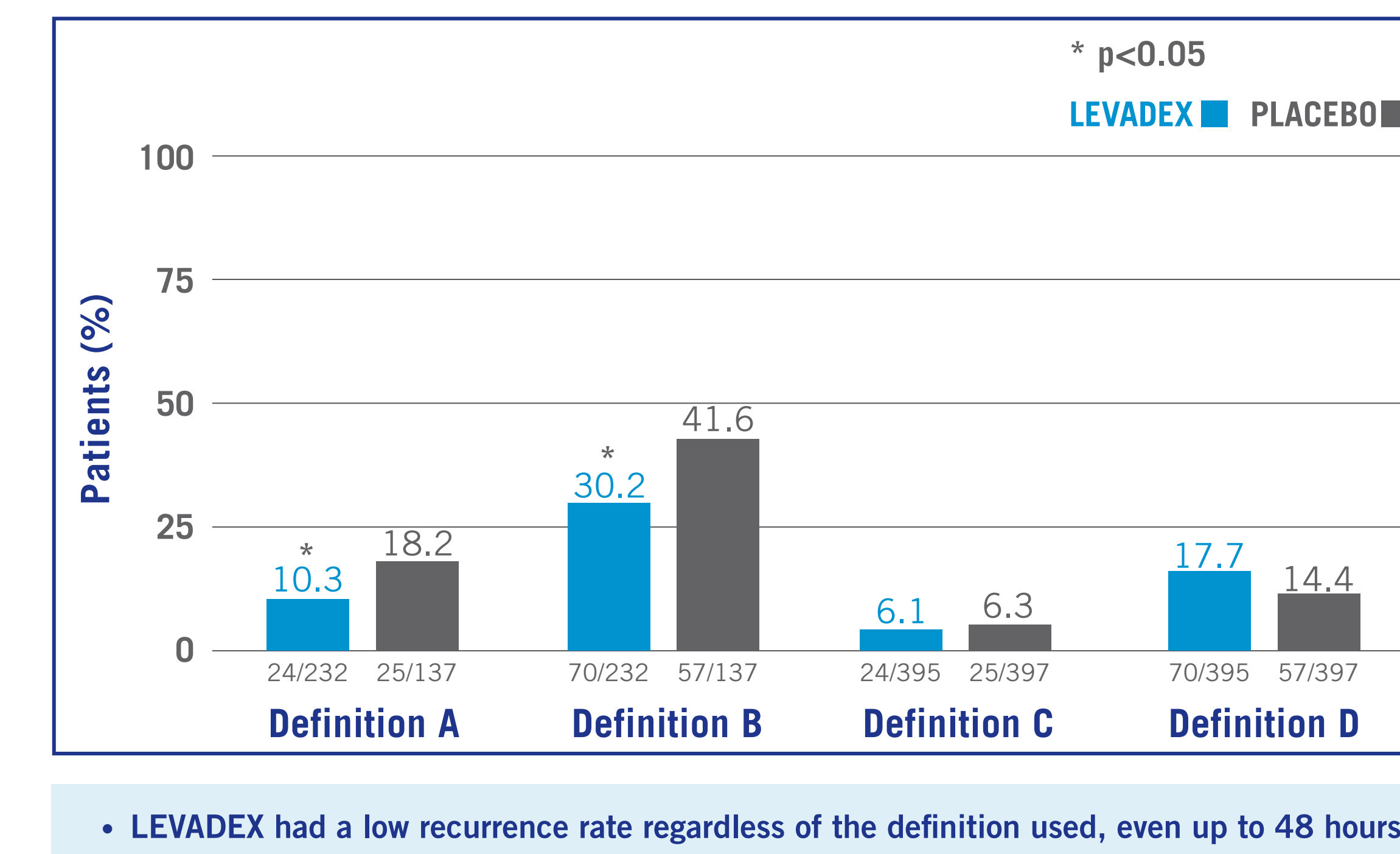
RECURRENCE OVER 24 HOURS

Figure 2. Recurrence over 24 hours



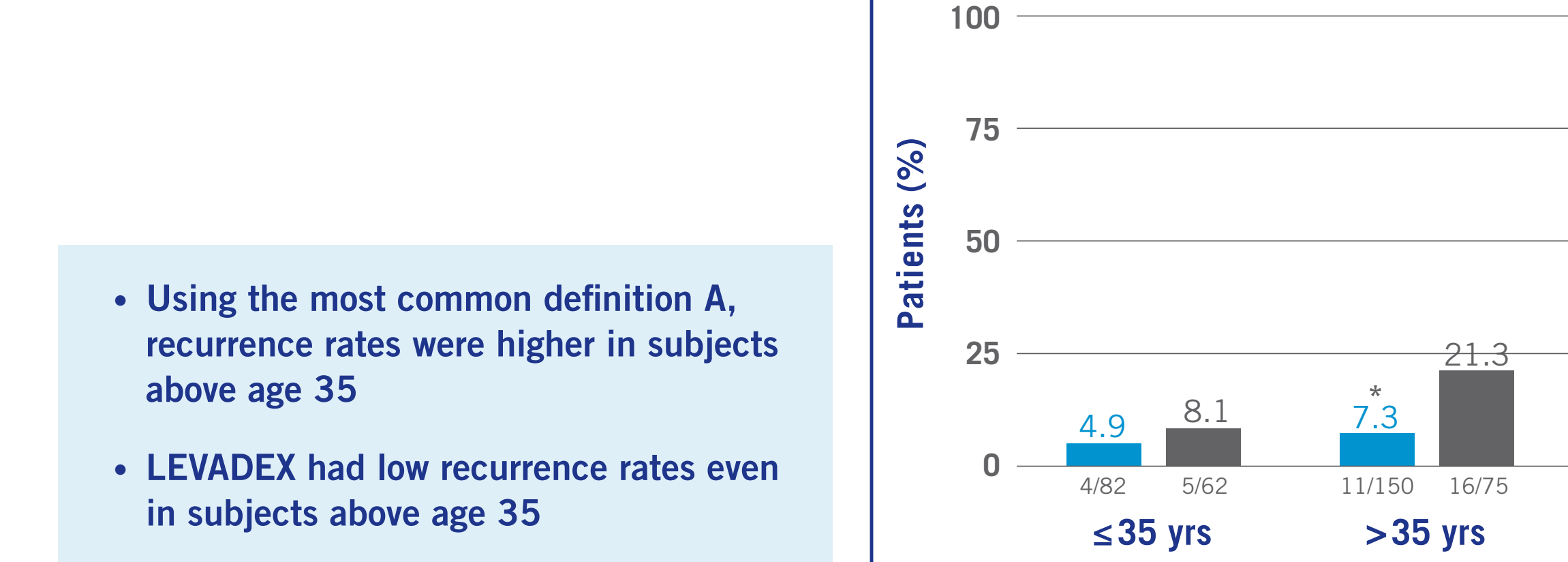
RECURRENCE OVER 48 HOURS

Figure 3. Recurrence over 48 hours



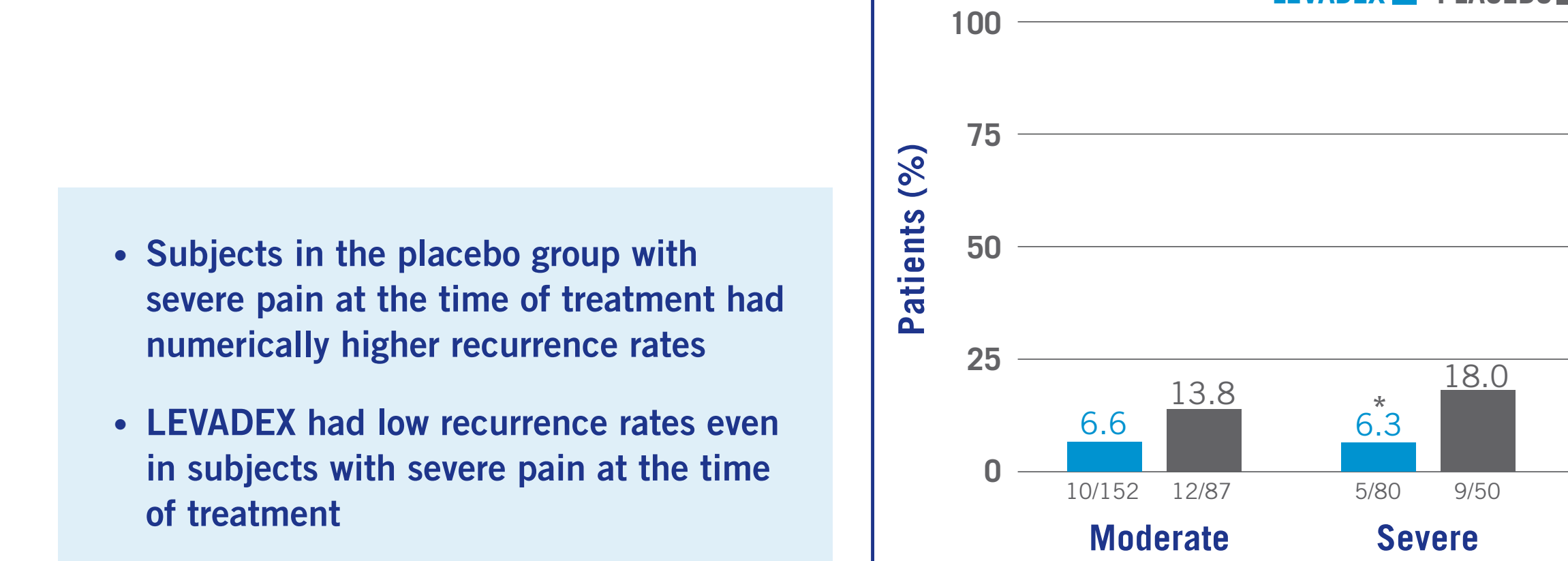
RECURRENCE BY AGE

Figure 4. Recurrence Rate over 24 Hours by Age, Using Definition A



RECURRENCE BY HEADACHE SEVERITY

Figure 5. Recurrence Rate over 24 Hours by Headache Severity, Using Definition A



DISCUSSION

As expected this analysis demonstrates a wide variability in the recurrence rates (3.8% to 22.4% over 24 hours) depending on the definition used. However there is no one standard method used to define recurrence rate. In fact the true definition, and the most stringent measure of recurrence rate, definition B, is rarely used in the literature. The most commonly used definition is A.

Two large meta analyses[3,5] using definition A have calculated the cumulative recurrence rate for triptans to be 22% and 29% within 24 hours. Using the same definition in our analysis the recurrence rate for LEVADEX was 6.5%. This is consistent with a previous study[8] that in a head to head comparison of DHE and sumatriptan demonstrated that DHE had a 2.5 times lower recurrence rate compared to sumatriptan over 24 hours. No similar data is available for triptan recurrence rates from 24 to 48 hours in the literature. However, caution should be exercised in evaluating and comparing these data as multiple other factors, including response rates at two hours, can alter the observed recurrence rate.

One of the meta analyses[5] showed a correlation between recurrence rate and age and sex of the patient and severity of the pain at the time of treatment. Female gender, age above 35 and severe pain at the time of treatment were risk factors for high recurrence rate. Our analysis confirmed that both age and severity of pain at time of treatment were associated with higher recurrence rates in the placebo group. However, LEVADEX demonstrated reduced recurrence rates regardless of age or severity of pain at the time of treatment. Given the complexities of the problem, it could be argued the best way to compare prolongation of effect would be a crossover study comparing a triptan to DHE, so as to reduce any possible effect of individual variation.

CONCLUSION

Recurrence rates, which many physicians rely on to assess the sustained effects of acute migraine therapies, can vary widely and can be deceptive depending on the specific definition used. A standardized definition should be developed to make such comparisons easy and meaningful. In a Phase 3 study, LEVADEX (orally inhaled DHE) demonstrated low recurrence rates regardless of the definition used.

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