

Topiramate Versus Amitriptyline for Migraine Prophylaxis: A Multicenter, Randomized, Double-Blind, Parallel Treatment Group Trial

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OBJECTIVES

- To compare the relative efficacy and safety profiles of topiramate (TPM) and amitriptyline (AMI) in the prophylaxis of migraine headache
- To determine the relative tolerability profiles, changes in weight, and the impact of treatment and weight changes on quality of life and other subject-reported outcomes

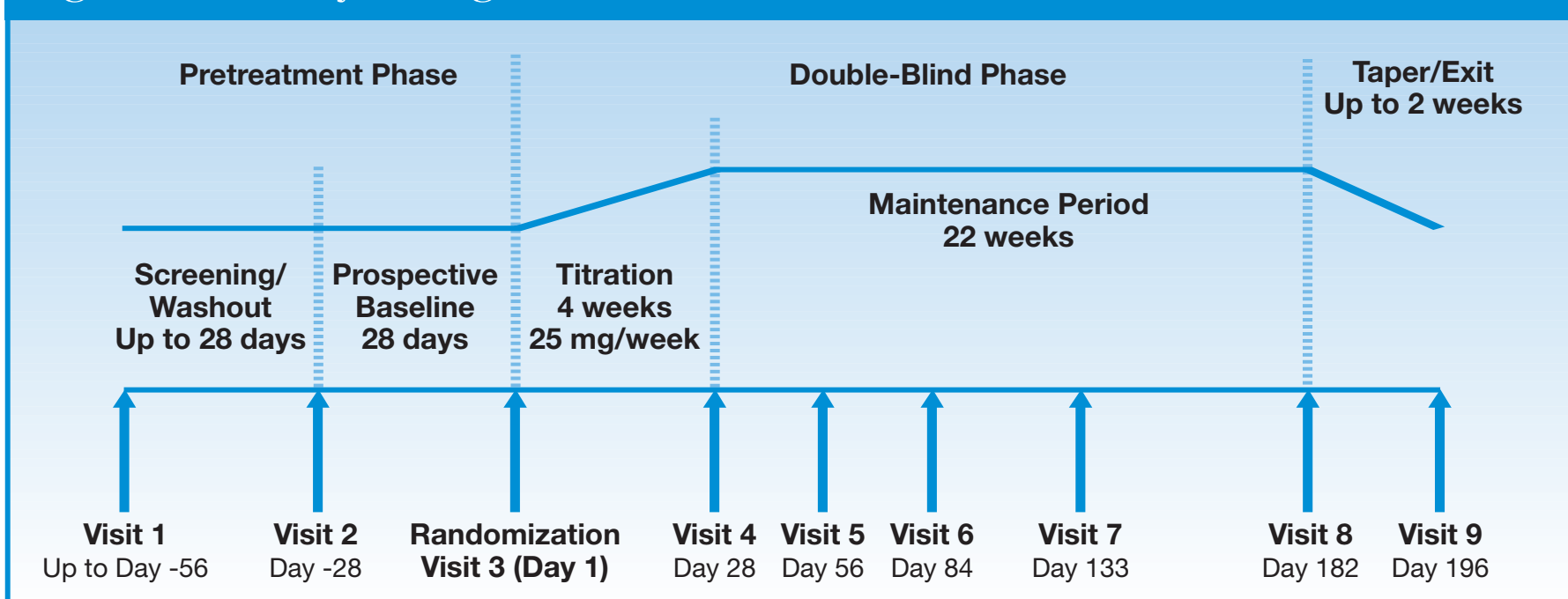
BACKGROUND

- TPM is an effective, safe, and generally well-tolerated migraine preventive medication, as demonstrated in several randomized, double-blind, placebo-controlled trials with over 1500 patients¹⁻³
 - TPM 100 mg/d is the recommended target dose for migraine prophylaxis, although lower or higher daily doses are effective for some individuals
 - In clinical trials, TPM has generally been either weight neutral or associated with weight loss
- Although this study was initiated prior to U.S. regulatory approval of TPM for migraine prophylaxis, TPM is now approved in 59 countries (including the U.S.) for the prophylaxis (prevention) of migraine headache in adults
- Results from limited clinical studies also suggest that AMI is effective for migraine prophylaxis, although AMI does not have regulatory approval for this indication⁴
- Weight gain can adversely impact the clinical course of migraine and medical health in general^{5,6}
- The consequences of obesity in adults include^{6,7}
 - An increased risk of morbidity and mortality from cardiovascular disease, stroke, diabetes, hypertension, and cancer (prostate, colon, breast, endometrial)
 - Dissatisfaction with treatment
 - Reduced treatment compliance
 - Diminished self-esteem

METHODS

- A multicenter, randomized, double-blind, parallel treatment group, comparative study of TPM 100 mg/d (50 mg BID) and AMI 100 mg/d (100 mg HS) in subjects with episodic migraine (N = 347; ≥18 years) (Figure 1). Starting dose for each drug was 25 mg/d, with weekly increments of 25 mg to a target dose of 100 mg/d at Day 28
- If possible, all medications used for migraine prophylaxis were discontinued prior to the start of the prospective baseline period
- Subjects must have maintained a dose of ≥50 mg/d of the assigned study medication in order to remain in the maintenance period
- In order to establish parity on efficacy as a basis for conducting additional pre-specified secondary analyses, a non-inferiority analysis based on migraine episode rate reduction was performed as the primary outcome variable
 - AMI was designated to be the active control in this non-inferiority analysis

Figure 1. Study Design



Key Inclusion/Exclusion Criteria

- Subjects had an established history of migraine headache, with or without aura (ICHD-II criteria), for ≥6 months and experienced approximately 3–12 migraine headaches per month for 3 months prior to entering the screening/washout period
- Subjects had 3–12 migraine episodes and ≤15 headache days (migraine or non-migraine) during the 28-day prospective baseline period
- Subjects were excluded if they had previously failed >2 adequate trials of migraine prophylactic medication or an adequate trial of TPM or AMI
- Subjects were excluded if they were taking any over-the-counter or prescribed medication having possible migraine preventive efficacy
- Subjects with medication overuse headache (MOH), cluster headache, or progressive neurologic disorders other than migraine were excluded

Primary Efficacy Variable (ITT Population)

- Change in average monthly (28-day) migraine episode rate from the prospective baseline to the double-blind phase

Secondary Efficacy Variables (ITT Population)

- Mean change from baseline in monthly (28-day) migraine headache days
- Mean change from baseline in monthly (28-day) total headache days
- Responder rates (≥25%, ≥50%, ≥75%, 100% reduction) in: migraine headache days and total headache days
- Change in monthly (28-day) rate of acute abortive medications used
- Change in monthly (28-day) migraine duration
- Change in average migraine severity
- Change in average severity of migraine-associated symptoms: nausea, photophobia, and phonophobia
- Change in monthly (28-day) frequency of: nausea, photophobia, and phonophobia
- Change in monthly (28-day) rate of vomiting during the attack

Quality-of-Life and Disability Questionnaires

- Migraine-Specific Quality-of-Life Questionnaire (MSQ)
 - Validated migraine-specific quality-of-life instrument; 4-week recall period
- One-item Functional Disability Question
 - Measures the worst level of disability associated with headaches that occurred; 1-day recall period
- Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF)
 - Scale not validated for migraine; provides general assessment of quality of life; 1-week recall period
- Migraine Disability Assessment (MIDAS)
 - Validated disability assessment tool for migraine; 3-month recall period

Safety Assessments

- Treatment-emergent adverse events (AEs), serious AEs

RESULTS

Figure 2. Subject Disposition and Reasons for Discontinuation

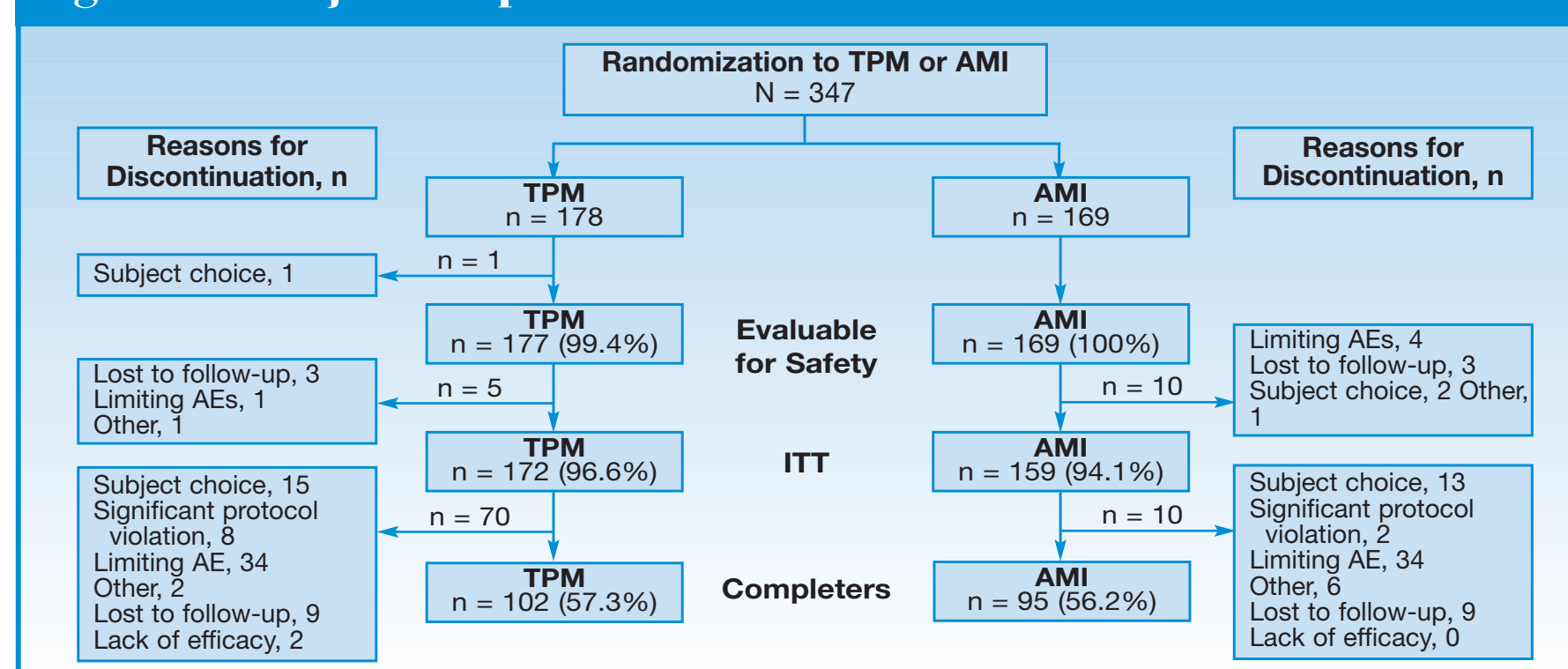


Table 1. Subject Demographics and Baseline Characteristics

	TPM n = 172	AMI n = 159
Age, years (mean ± SD)	39.7 ± 10.7	37.9 ± 11.3
Gender, n (%)		
Male	23 (13.4)	27 (17.0)
Female	149 (86.6)	132 (83.0)
Race, n (%)		
White	143 (83.1)	137 (86.2)
Black	23 (13.4)	15 (9.4)
Other	6 (3.5)	7 (4.4)
Weight (kg)		
Mean ± SD	76.6 ± 19.5	77.4 ± 21.2
Median	72.8	73.9
BMI (kg/m ²)		
Mean ± SD	27.7 ± 6.8	28.5 ± 7.8
Median	26.1	26.8

Table 2. Percentage of Subjects by BMI Categories

BMI Category	BMI Range (kg/m ²)	Subjects in the Study N (%)		
		TPM n = 172	AMI n = 159	All N = 331
Underweight	<18.5	5 (2.9%)	2 (1.3%)	7 (2.1%)
Normal	18.5 to <25	69 (40.1%)	58 (36.5%)	127 (38.4%)
Overweight	25 to <30	40 (23.3%)	45 (28.3%)	85 (25.7%)
Obese	30 to <35	33 (19.2%)	32 (20.1%)	65 (19.6%)
Severely obese	≥35	24 (14.0%)	22 (13.8%)	46 (13.9%)
Missing		1 (0.6%)	0 (0.0%)	1 (0.3%)

Figure 3. Mean Change From Baseline in Monthly (28-Day) Migraine Episode Rate (ITT Population)

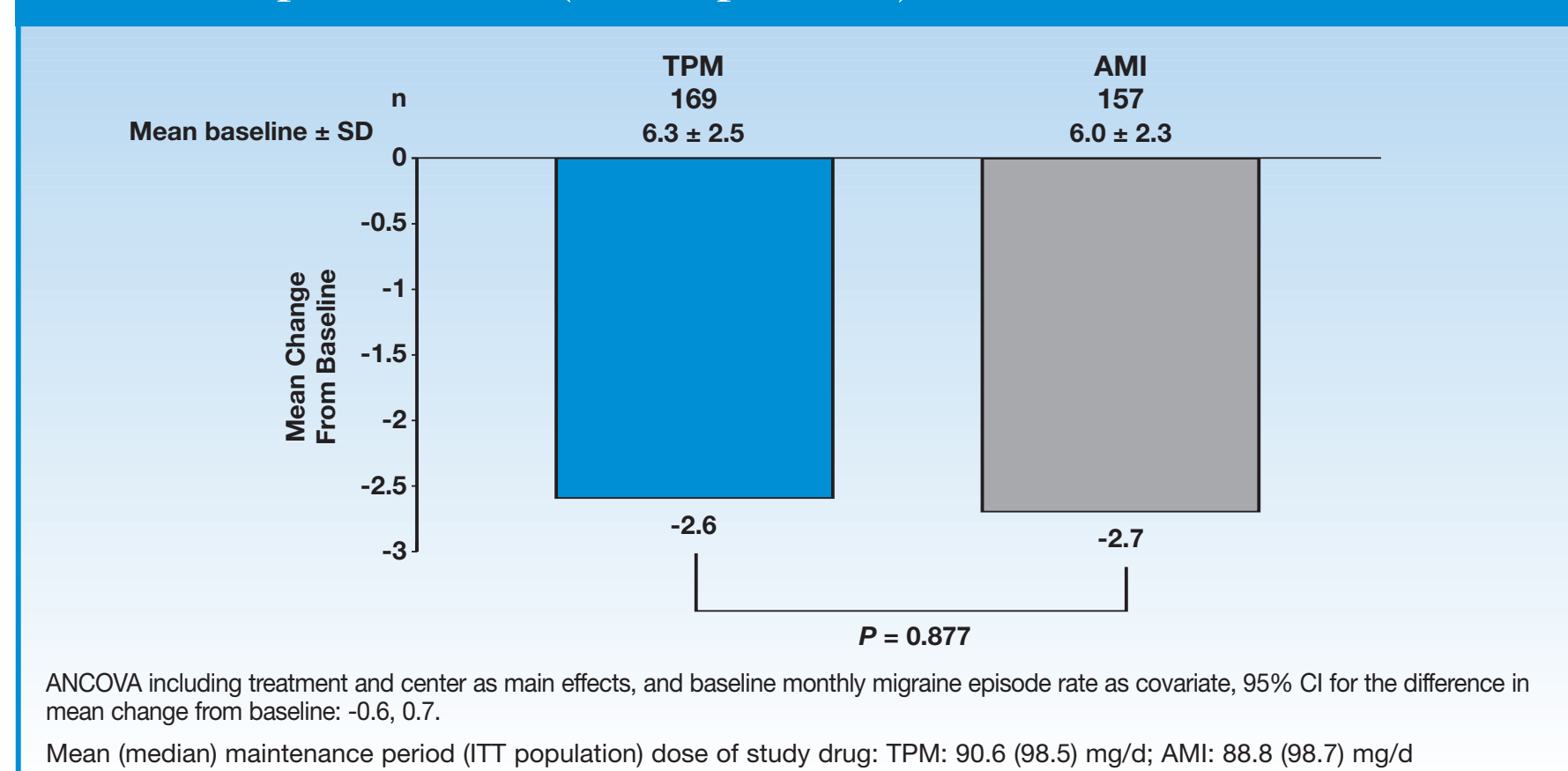
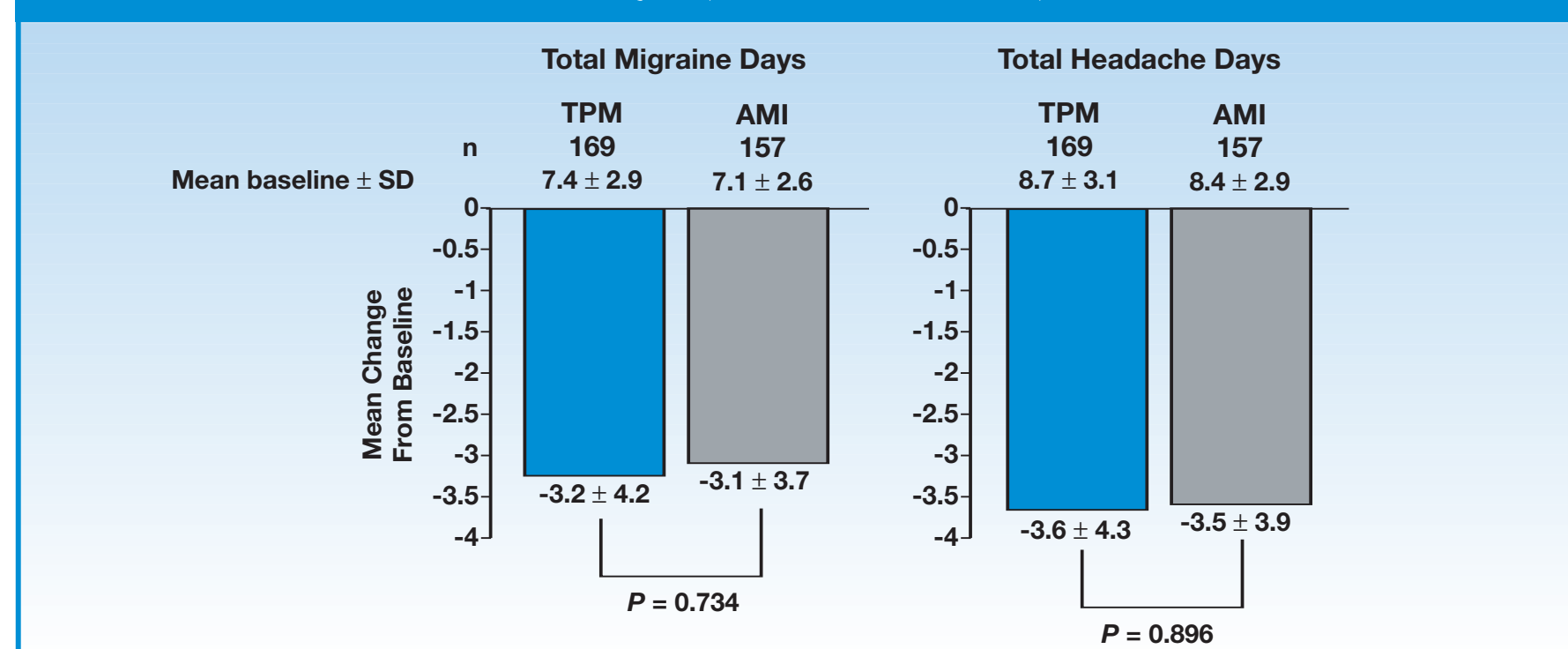


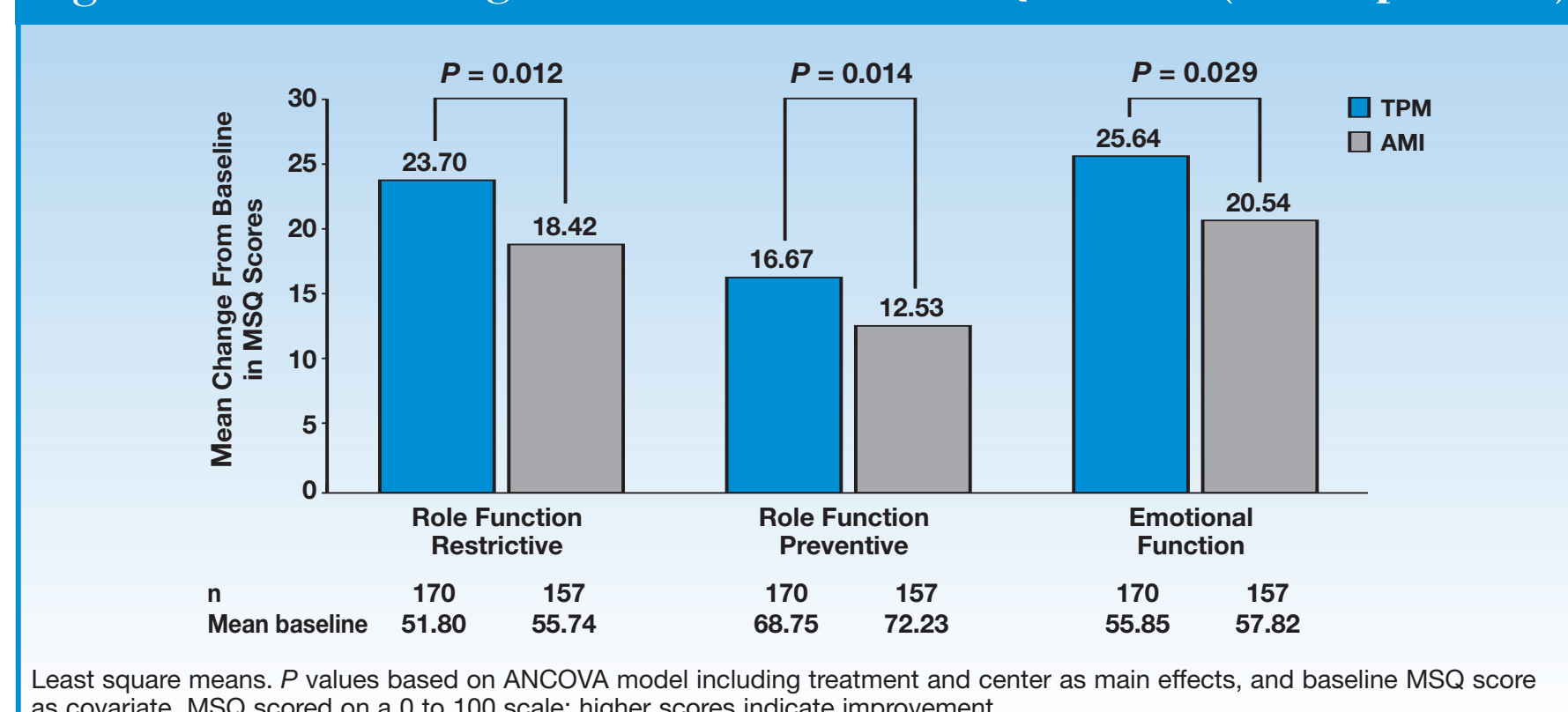
Figure 4. Mean Change From Baseline in Rate of Total Migraine Days and Headache Days (ITT Population)



Secondary efficacy variables (ITT population):

- Responder rates (≥25%, ≥50%, ≥75%, 100% reduction) in
 - Migraine headache days (P = 0.903 [≥25%], 0.096 [≥50%], 0.241 [≥75%], 0.805 [100%])
 - Total headache days (P = 1.000 [≥25%], 0.061 [≥50%], 0.073 [≥75%], 0.788 [100%])
- Change in monthly (28-day) rate of acute abortive medications used (P = 0.475)
- Change in monthly (28-day) migraine duration (P = 0.870)
- Change in average migraine severity (P = 0.948)
- Change in average severity of migraine-associated symptoms:
 - Nausea (P = 0.795), photophobia (P = 0.801), phonophobia (P = 0.998)
- Change in monthly (28-day) frequency of:
 - Nausea (P = 0.937), photophobia (P = 0.714), phonophobia (P = 0.698)
- Change in monthly (28-day) rate of vomiting during the attack (P = 0.690)

Figure 5. Mean Change From Baseline in MSQ Scores (ITT Population)



Study supported by Ortho-McNeil Neurologics, Inc.

- Results of specified quality-of-life and disability scales comparing mean changes from baseline were as follows for TPM vs AMI treatment (ITT population)
 - Functional Disability Question: change in average severity of functional disability was TPM (-0.33) vs AMI (-0.19), P = 0.047
 - Q-LES-Q-SF: improvement in score for TPM (4.56) vs AMI (4.63), P = 0.959
 - Interpretation of this result must take into consideration that this scale is very general and is not treatment- or condition-specific as subjects were asked to "take everything into consideration" when completing it
 - In addition, the recall period of 1 week is likely not ideal for a condition that is episodic in nature
 - MIDAS: improvement score for TPM (-12.3) vs AMI (-14.3), P = 0.288
 - This result requires cautious interpretation due to a substantial number of subjects with missing follow-up assessment data
 - In addition, some of the subjects included in the analysis may have had an overlap in the recall period between baseline and follow-up assessments

Figure 6. Categorical Changes in Weight From Baseline (ITT Population)

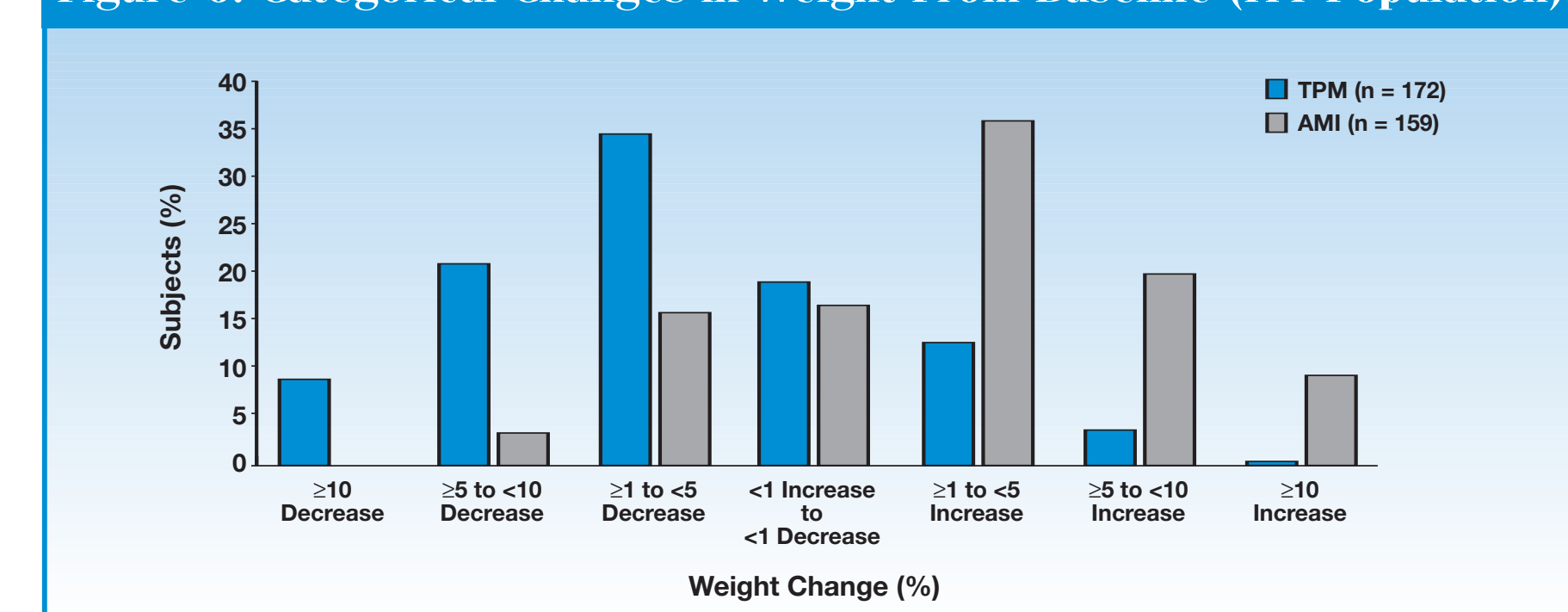


Table 3. Number of Subjects* Experiencing a Shift in BMI From Baseline to Double-Blind Phase

BMI	TPM (n = 177) Endpoint					AMI (n = 169) Endpoint				
	<18.5	18.5 to <25	25 to <30	30 to <35	≥35	<18.5	18.5 to <25	25 to <30	30 to <35	≥35
Baseline <18.5	5 (2.8%)					1 (0.6%)				
18.5 to <25	5 (2.8%)	64 (36.2%)				50 (29.6%)	8 (4.7%)			
25 to <30		10 (5.6%)	29 (16.4%)			35 (20.7%)	8 (4.7%)	1 (0.6%)		
30 to <35			14 (7.9%)	19 (10.7%)		5 (3.0%)	22 (13.0%)	5 (3.0%)		
≥35				3 (1.7%)	20 (11.3%)			2 (1.2%)	20 (11.3%)	

*Subjects without a second BMI measurement were excluded (TPM: n = 6; AMI: n = 11). Green indicates a shift to a lower BMI category; red indicates a shift to a higher BMI category.

Table 4. The Five Most Common Treatment-Emergent AEs

TPM	n (%)	AMI	n (%)
Paresthesia	53 (29.9)	Dry mouth	60 (35.5)
Fatigue	30 (16.9)	Fatigue	41 (24.3)
Somnolence	21 (11.9)	Somnolence	30 (17.8)
Hypoesthesia	19 (10.7)	Weight gain	23 (13.6)
Nausea	18 (10.2)	Dizziness, Sinusitis (tie)	18 (10.7)
Patients with any AE	152 (85.9)	Patients with any AE	150 (88.8)

- Any AE causing withdrawal from the study
 - TPM: 35 (19.8%); AMI: 38 (22.5%)
- Any serious AEs (SAEs)
 - TPM (subjects with any SAE, n = 4): accidental injury with ecchymosis, dysmenorrhea/menorrhagia/ovarian disorder/ vaginal hemorrhage, n = 3
 - AMI (subjects with any SAE, n = 7): migraine aggravated, n = 1; esophagitis, n = 1; cholecystitis, n = 1; brain neoplasm, benign/breast neoplasm, malignant, n = 2; menorrhagia, n = 1; renal calculus, n = 1

CONCLUSIONS

- The non-inferiority analysis demonstrated that TPM was at least as effective as AMI for the mean monthly reduction of migraine episode rate
- There were no statistically significant between-group differences on prespecified secondary efficacy variables
- TPM-treated subjects achieved improvement in all 3 domains of the MSQ, as well as reduction in average severity of functional disability based on the Functional Disability Question, that were statistically superior to those achieved by AMI-treated subjects
- Improvements in the Q-LES-Q-SF and MIDAS were similar in both treatment groups, although these results require cautious interpretation
- 64.6% of AMI-treated subjects (ITT) gained ≥1% body weight and 28.5% gained ≥5% body weight during the 26-week double-blind treatment period vs 17.0% and 4.1%, respectively, for TPM-treated subjects
- 64.4% of TPM-treated subjects (ITT) lost ≥1% body weight and 29.9% lost ≥5% body weight during the 26-week double-blind treatment period vs 19.0% and 3.2%, respectively, for AMI-treated subjects
- The safety and tolerability profiles were consistent with expectation for both medicines at the doses used
- The effects of weight change on treatment efficacy and tolerability, quality-of-life measures, and laboratory measures are unknown. Post hoc analyses to determine any potential associations are planned

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