

Naturalistic Study of Mixed Amphetamine Salts Extended Release for Adult ADHD

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ABSTRACT

Objective: Evaluate the safety and efficacy of mixed amphetamine salts extended release (MAS XR) in adults with attention-deficit/hyperactivity disorder (ADHD).

Methods: This phase was a 10-week interim analysis of the Quality of life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) trial, an ongoing, 30-week, open-label, multicenter investigation of once-daily MAS XR (10–60 mg/d) in adults (≥18 years of age) with ADHD in community practice settings.

Results: With up to 10 weeks of open-label MAS XR 10 to 60 mg/d, 725 adults exhibited improvement within 1 week and sustained improvement in ADHD symptoms throughout the study. At end point, significant decreases from baseline were seen in ADHD Rating Scale (RS) total scores (-19.8 ± 11.6 ; $P < .0001$), hyperactivity/impulsivity (-8.1 ± 6.1 ; $P < .0001$), and inattentiveness (-11.6 ± 6.7 ; $P < .0001$). Most subjects (74.4%) were rated as much/very much improved. Significant improvements ($P < .0001$) in quality of life (QOL) were seen in all domains of the 36-Item Short-Form Health Survey Version 2.0 (SF-36v2) except bodily pain ($P = .1431$). Few subjects (50/725, 6.9%) withdrew due to adverse events (AEs); the most common MAS XR-related AEs were decreased appetite (19.2%), dry mouth (19.2%), insomnia (17.8%), and headache (16.8%).

Conclusions: In adults with ADHD, MAS XR treatment is generally safe, with significant improvements observed in ADHD symptoms and related QOL.

INTRODUCTION

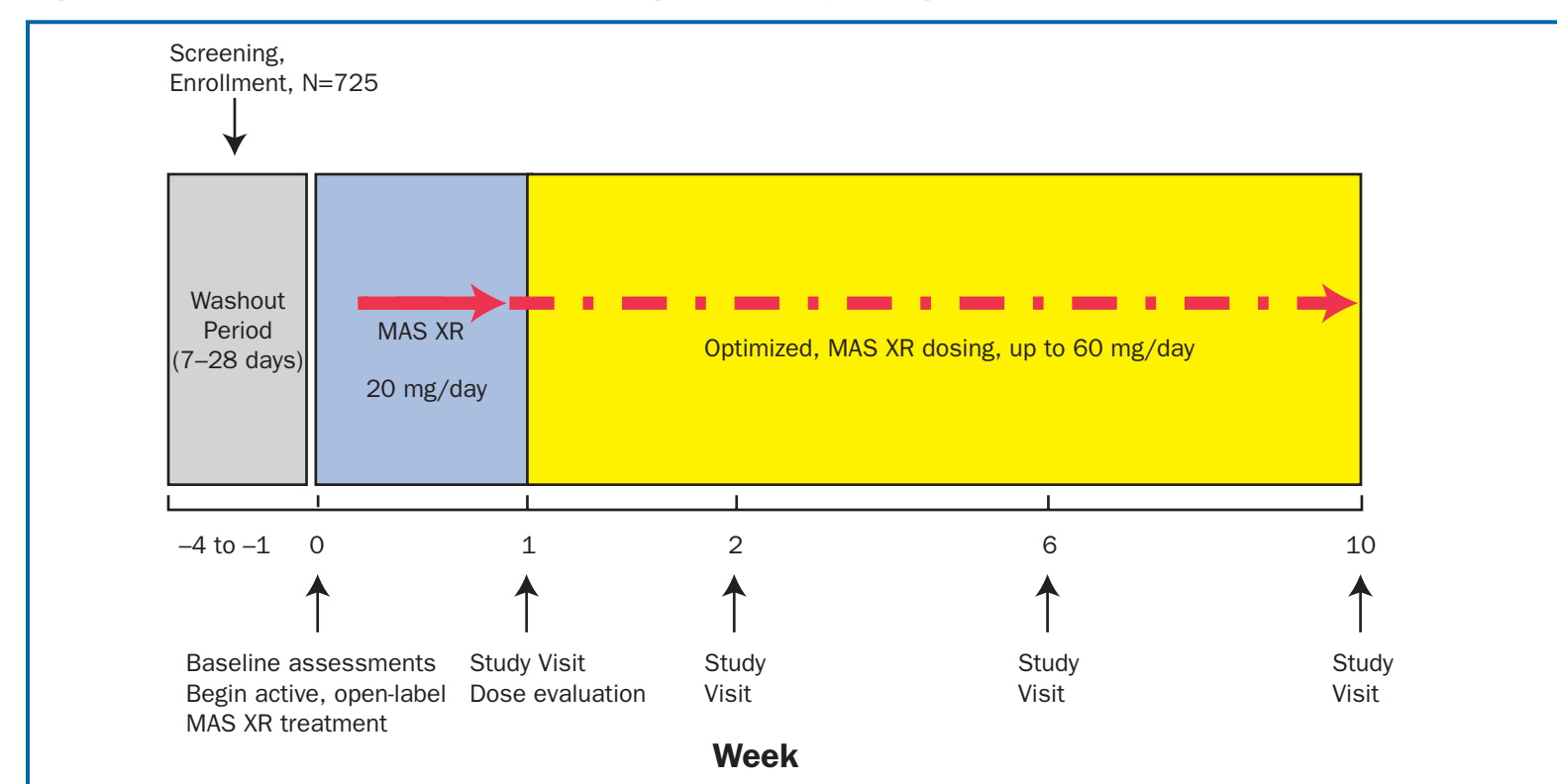
- Clinically significant symptoms of ADHD persist into adolescence and adulthood,^{1,2} and as many as 6 to 10 million adults may be diagnosed with ADHD.³
- Controlled studies in adults with ADHD show stimulant response rates of more than 70% in those given adequate doses.^{4,5}
- Sustained efficacy with MAS XR given for up to 24 months was recently reported in a large study of adult patients (n=255) with combined subtype ADHD. (Data on file, Shire Pharmaceuticals Inc.)
- To better examine the results of pharmacologic treatment in a broader sample of adults with ADHD, the QU.E.S.T. trial has been undertaken.
- The primary objective of the QU.E.S.T. trial is to analyze the safety and efficacy of MAS XR (optimized, open-label doses) in a large sample of adults with ADHD drawn from naturalistic, community-practice settings.
- The trial consists of 2 phases: a 10-week core phase and an additional 20-week extension phase. The results of the 10-week core investigation are presented here.

METHODS

QU.E.S.T. Study Design

- This was a 10-week, multicenter, open-label investigation of MAS XR (10–60 mg/d) in adults with ADHD (Figure 1).
- Subjects were given MAS XR 20 mg/d for 1 week. Based on investigator judgment, doses could then be increased or decreased by 10 mg to a minimum dose of 10 mg/d or a maximum dose of 60 mg/d to achieve optimal therapeutic response.
- Subjects were categorized according to previous ADHD treatment: (1) no previous treatment; (2) previous stimulant treatment; or (3) previous nonstimulant treatment.

Figure 1. QU.E.S.T. 10-Week Core Investigation Study Design



Main Inclusion Criteria

- Adults (≥18 years of age) with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR™)-based diagnosis of ADHD (combined subtype, predominantly inattentive subtype, predominantly hyperactive/impulsive subtype, or not otherwise specified).

Main Exclusion Criteria

- Comorbid symptomatic psychiatric condition, such as any severe axis I disorder or any axis II disorder.
- History of failure to respond to adequate doses of amphetamines.
- Recent history (within the past 6 months) or suspicion of substance abuse or a positive urine drug result at screening.
- Significant medical illness or history of seizure disorder within the last 2 years, tic disorder, Tourette syndrome, abnormal thyroid function, or cardiac disorder.
- Pregnancy or lactation.
- Clinically significant laboratory, vital sign, or electrocardiographic (ECG) abnormalities at baseline or screening.

RESULTS

Subject Disposition and Baseline Characteristics

- A total of 725 subjects enrolled in the study.
- Of these, 583 (80%) subjects completed the 10-week study; 23 (3%) withdrew consent, 50 (7%) withdrew because of AEs, and 69 (10%) withdrew for other reasons (including protocol violations and loss to follow-up). In all, 702 subjects met criteria for inclusion in the intent-to-treat (ITT) population.
- The 3 previous treatment subgroups were comparable at baseline with regard to demographic and clinical characteristics (Table 1).

Table 1. Baseline Demographic and Clinical Characteristics

	No Previous Treatment	Previous Stimulant Treatment	Previous Nonstimulant Treatment	Total
Enrolled subjects, n	387	281	57	725
ITT, n	378	272	52	702
Age (y), mean ± SD	37.7 ± 10.5	35.7 ± 12.2	38.2 ± 9.0	36.9 ± 11.1
Age category				
18–30 y	110	106	10	226
31–45 y	185	102	32	319
>45 y	92	73	15	180
Sex, n (%)				
Female	212 (55)	137 (49)	25 (44)	374 (52)
Male	175 (45)	144 (51)	32 (56)	351 (48)
Race, n (%) white	338 (87.3)	259 (92.2)	47 (82.5)	644 (88.8)
ADHD subtype, n (%)				
Combined	221 (57.1)	145 (51.6)	39 (68.4)	405 (55.9)
Inattentive	154 (39.8)	121 (43.1)	16 (28.1)	291 (40.1)
Hyperactive/Impulsive	9 (2.3)	14 (5.0)	1 (1.8)	24 (3.3)
Not specified	3 (0.8)	1 (0.4)	1 (1.8)	5 (0.7)
Baseline ADHD-RS, unit points (mean ± SD)				
Total score	33.0 ± 9.7	31.9 ± 10.1	36.7 ± 8.3	32.8 ± 9.8
Hyperactivity/Impulsivity	13.5 ± 6.3	13.0 ± 6.3	15.3 ± 5.9	13.5 ± 6.3
Inattentiveness	19.4 ± 5.0	18.9 ± 5.6	21.4 ± 4.1	19.4 ± 5.2

MAS XR Dosing

- At study visit 2, mean dose for the entire cohort was 19.3 mg/d, which reflects treatment initiation of all subjects with MAS XR 20 mg/d.
- Mean MAS XR doses given throughout the study are summarized in Table 2.

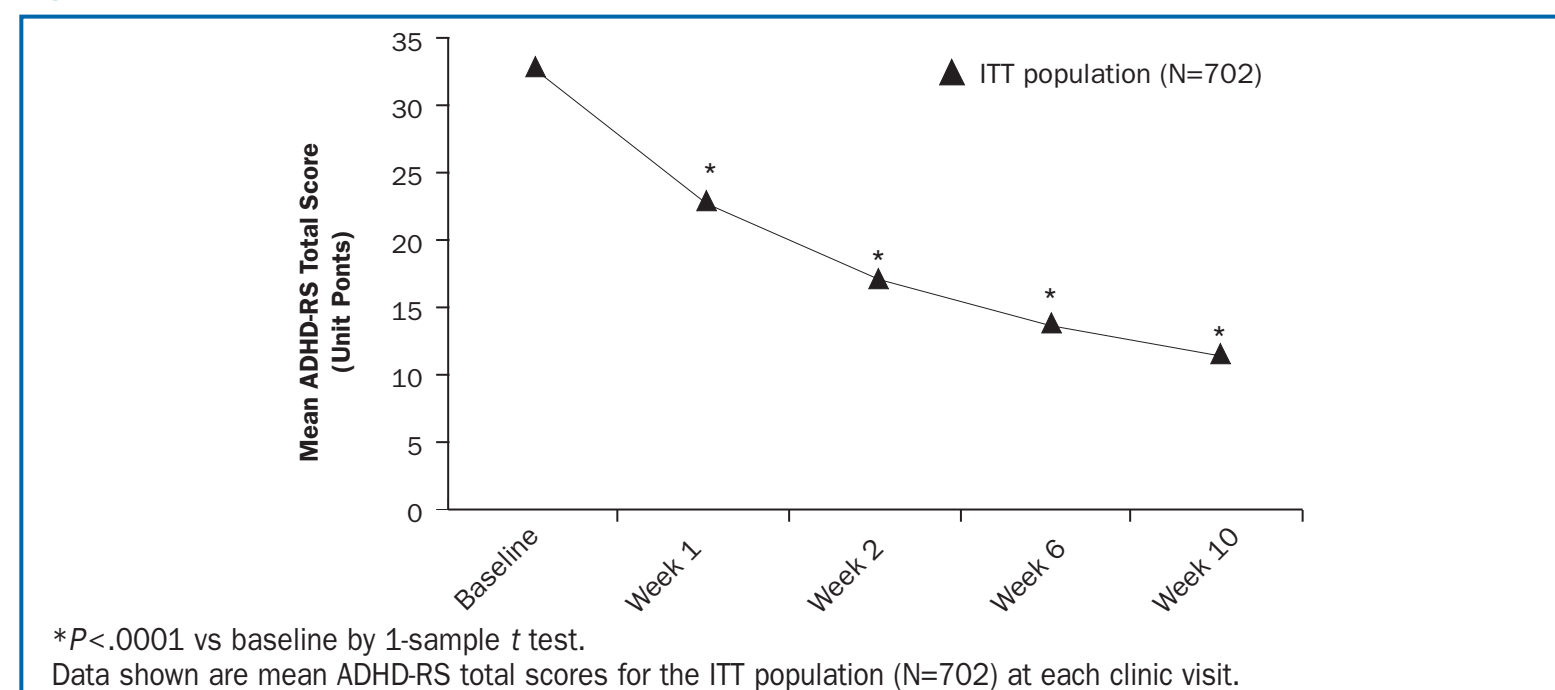
ADHD Efficacy Outcomes

- Figure 2 illustrates mean ADHD-RS total scores observed throughout the study in the ITT population.
- During week 1 of treatment when all subjects received MAS XR 20 mg/d, statistically significant improvements from baseline ADHD-RS total scores emerged ($P < .0001$), and continuing improvements were seen throughout the remainder of the 10-week study period (Figure 2).

Table 2. MAS XR Dosing During the QU.E.S.T. 10-Week Core Investigation (ITT Cohort, N=702)

Study Week, Mean Dose (SD), mg/d	Total Cohort (N=702)	No Previous Treatment (n=378)	Previous Stimulant Treatment (n=272)	Previous Nonstimulant Treatment (n=52)
Week 1	19.6 (3.7)	19.2 (3.5)	20.2 (3.6)	19.6 (5.4)
Week 2	29.3 (10.2)	27.6 (10.1)	31.6 (9.9)	30.3 (10.7)
Week 6	35.6 (18.2)	32.9 (20.5)	38.6 (14.1)	39.2 (17.1)
Week 10	37.2 (15.4)	34.9 (15.2)	39.9 (15.1)	39.7 (16.1)
Total	32.4 (12.5)	30.2 (11.9)	35.1 (12.4)	34.4 (13.9)

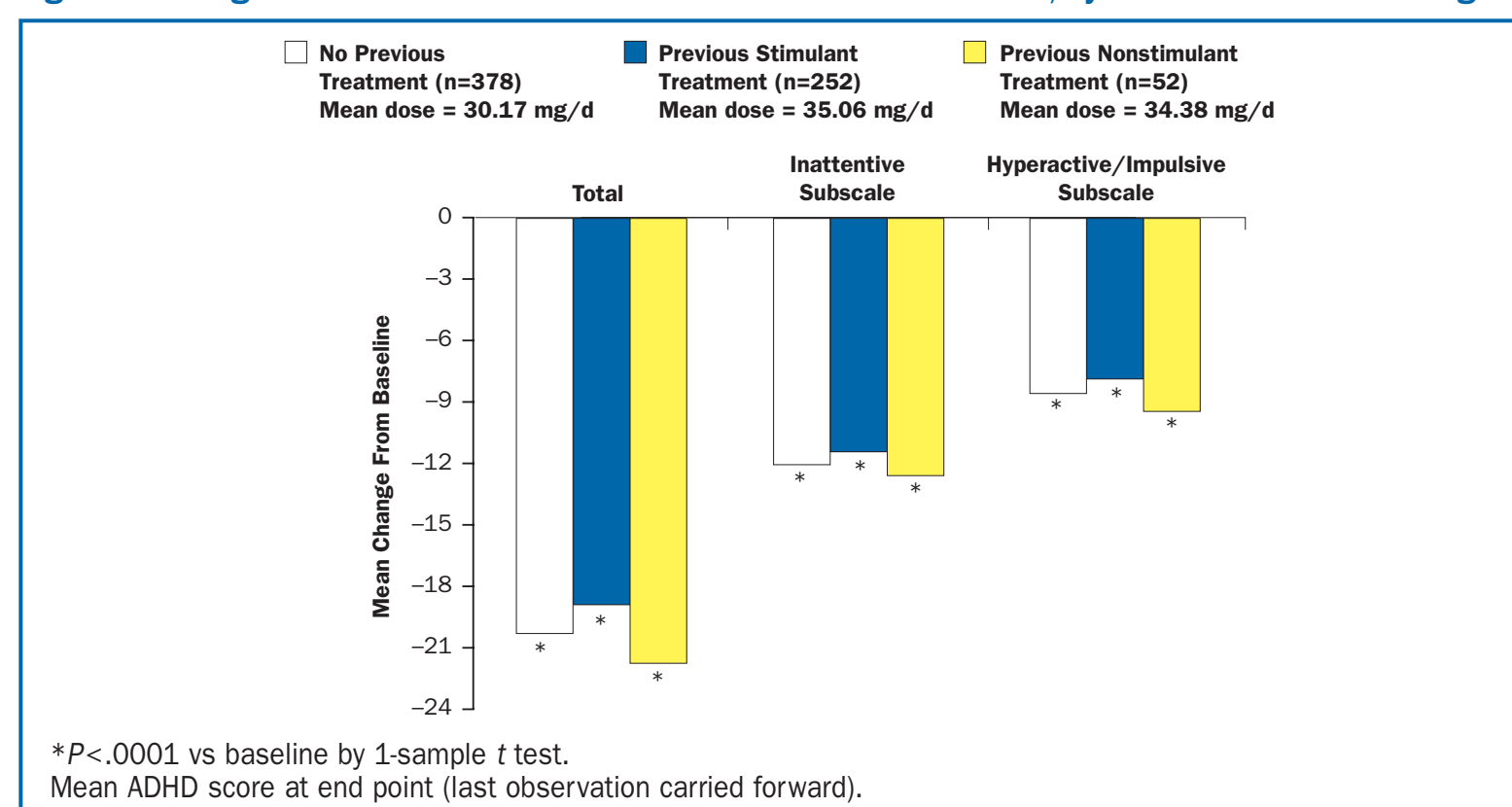
Figure 2. Mean ADHD-RS Total Scores (Unit Points)



* $P < .0001$ vs baseline by 1-sample t test. Data shown are mean ADHD-RS total scores for the ITT population (N=702) at each clinic visit.

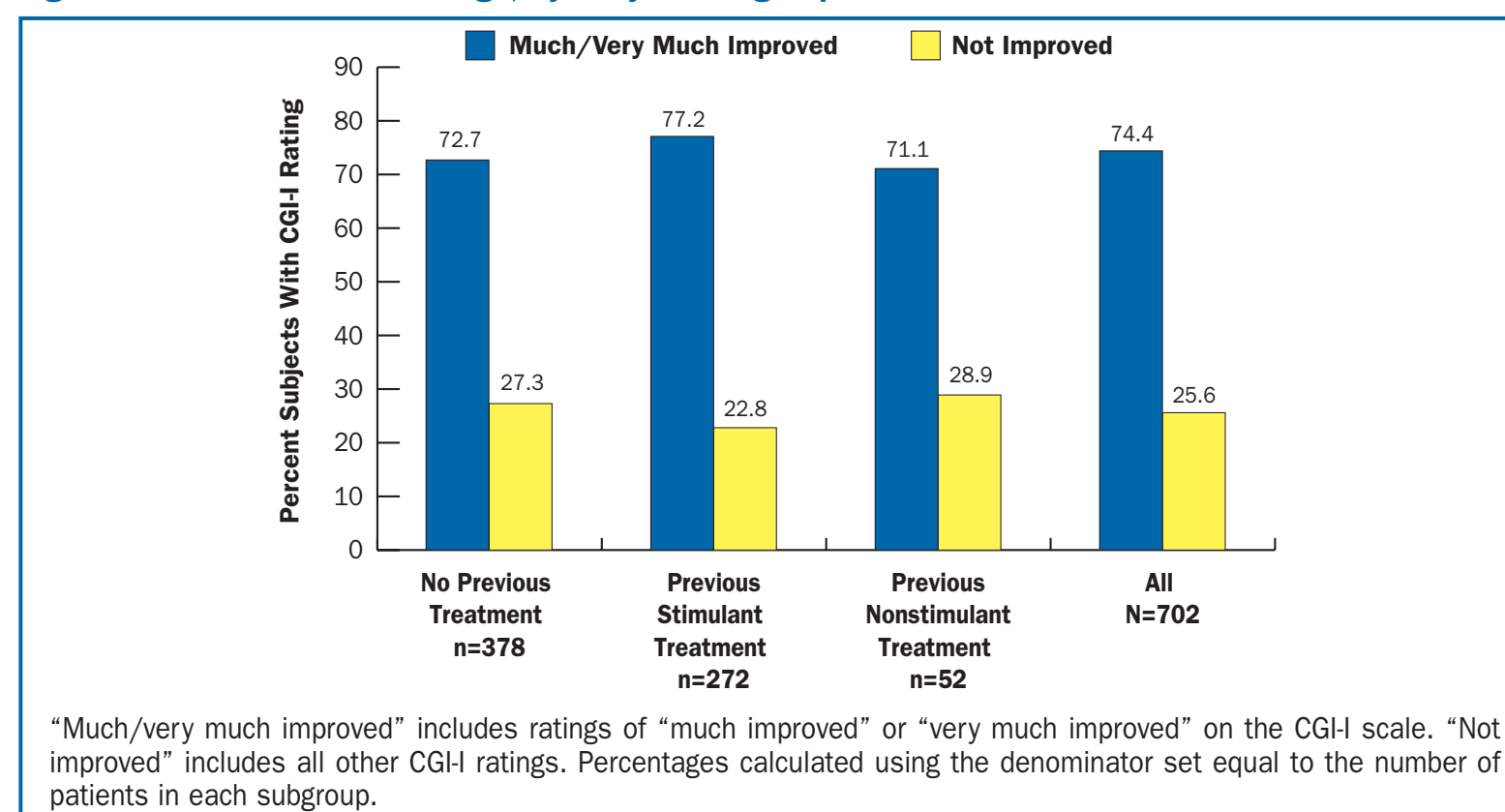
- At study end point, significant decreases from baseline were seen in ADHD-RS total scores, as well as subscale scores for hyperactivity/impulsivity and inattentiveness among both the total cohort and the previous treatment subgroups (Figure 3).

Figure 3. Change From Baseline to End Point in Mean ADHD-RS Scores, by Previous Treatment Subgroup



- At study end point, regardless of previous treatment subgroup, the majority of subjects obtained CGI-I ratings of much improved/very much improved (Figure 4).

Figure 4. End Point CGI-I Ratings, by Subject Subgroup



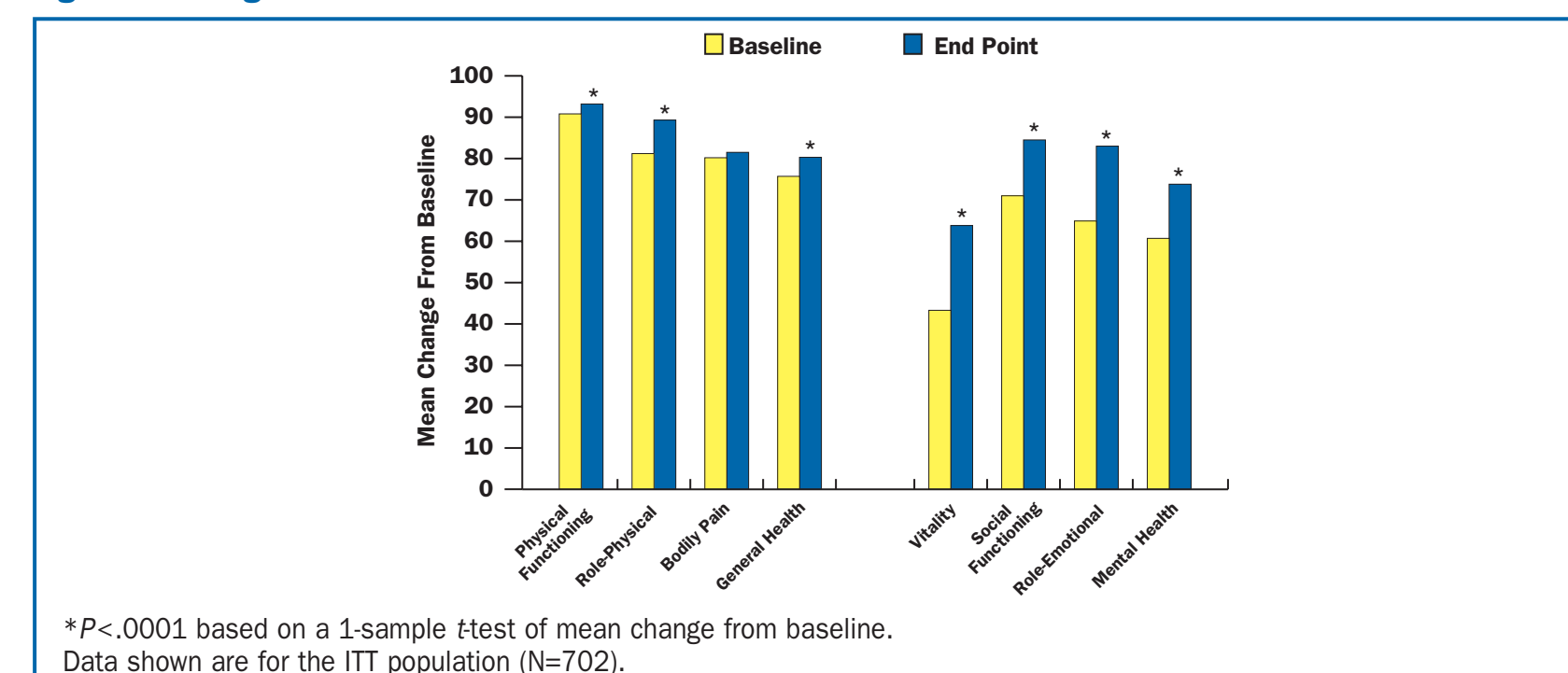
*'Much/very much improved' includes ratings of 'much improved' or 'very much improved' on the CGI-I scale. 'Not improved' includes all other CGI-I ratings. Percentages calculated using the denominator set equal to the number of patients in each subgroup.

- Only 6 subjects (6 of 702, 0.9%) were considered much worse, and no subjects were considered very much worse at end point.

QOL Outcomes

- At study end point, subjects reported significant improvement from baseline (all $P < .0001$) in all QOL domains measured by the SF-36v2 except bodily pain ($P = .1431$; Figure 5).
- A similar pattern of results was seen among the previous treatment subgroups (data not shown).

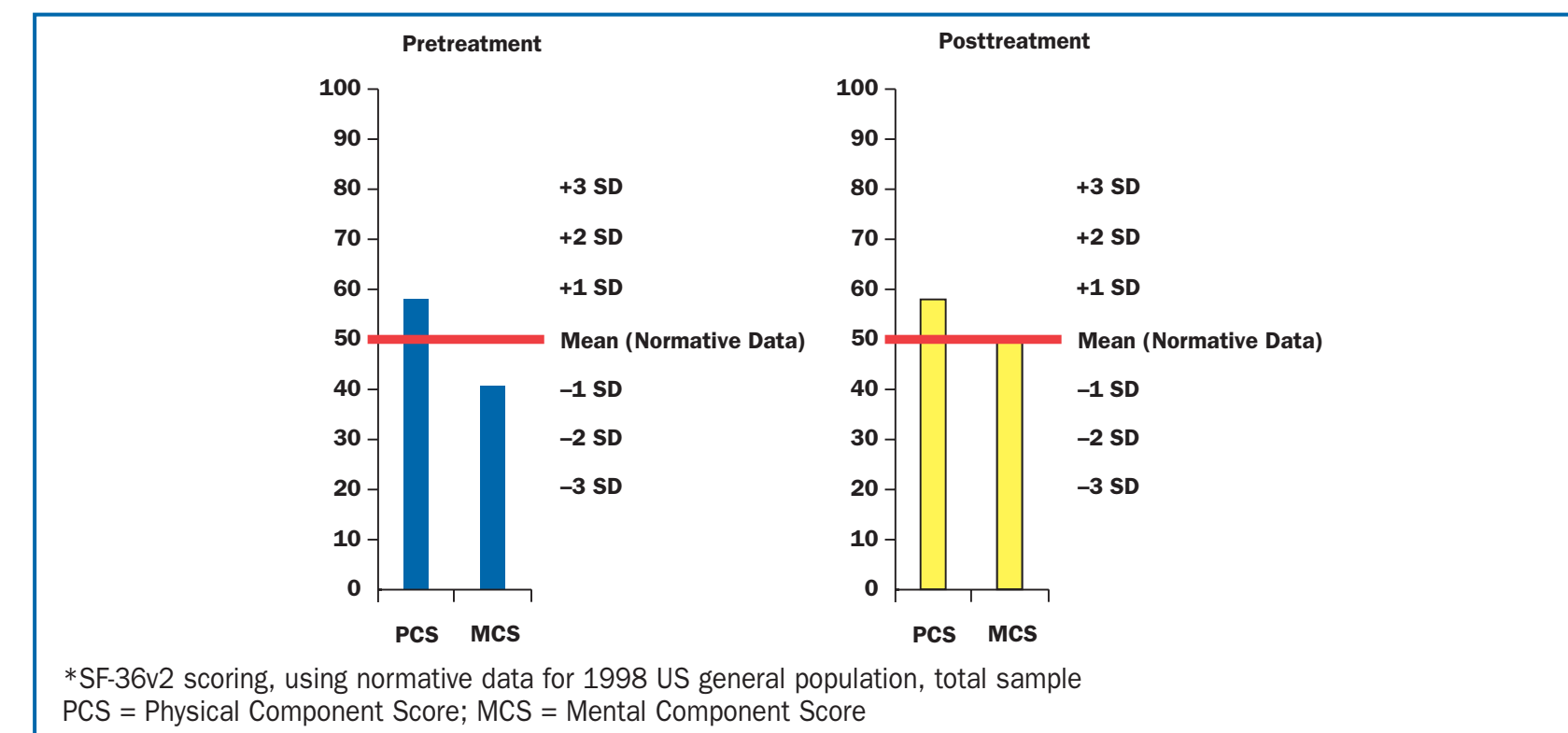
Figure 5. Change From Baseline to End Point in Mean SF-36v2 Scores



* $P < .0001$ based on a 1-sample t test of mean change from baseline. Data shown are for the ITT population (N=702).

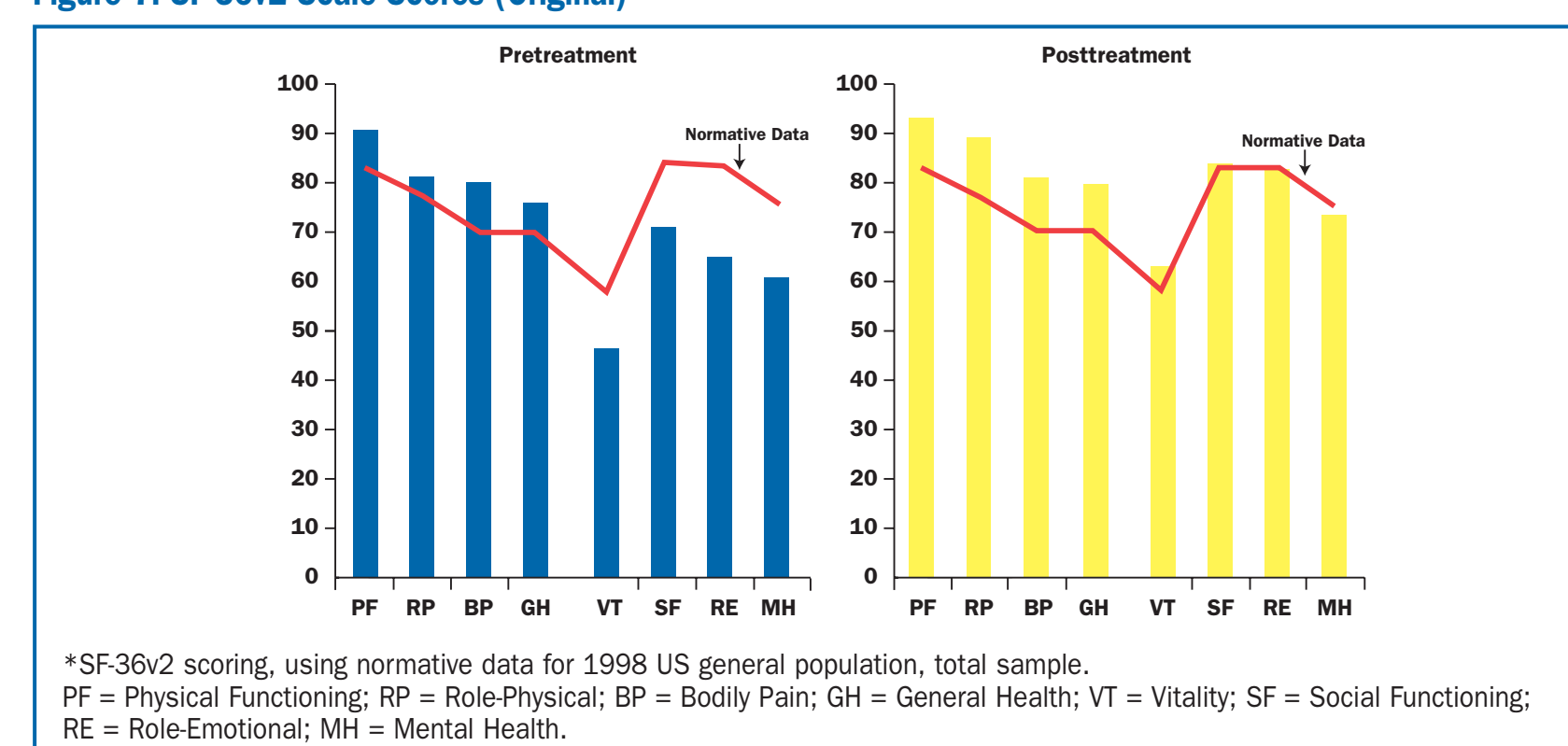
- Figures 6–8 show improvements in mental functioning following treatment with MAS XR. Pretreatment SF-36v2 scores that were considered impaired (compared with normative data) improved to within the normal range following treatment; physical functioning was not considered impaired prior to treatment compared with normative data in this patient population.

Figure 6. SF-36v2 Pretreatment and Posttreatment Summaries*



*SF-36v2 scoring, using normative data for 1998 US general population, total sample. PCS = Physical Component Score; MCS = Mental Component Score.

Figure 7. SF-36v2 Scale Scores (Original)*

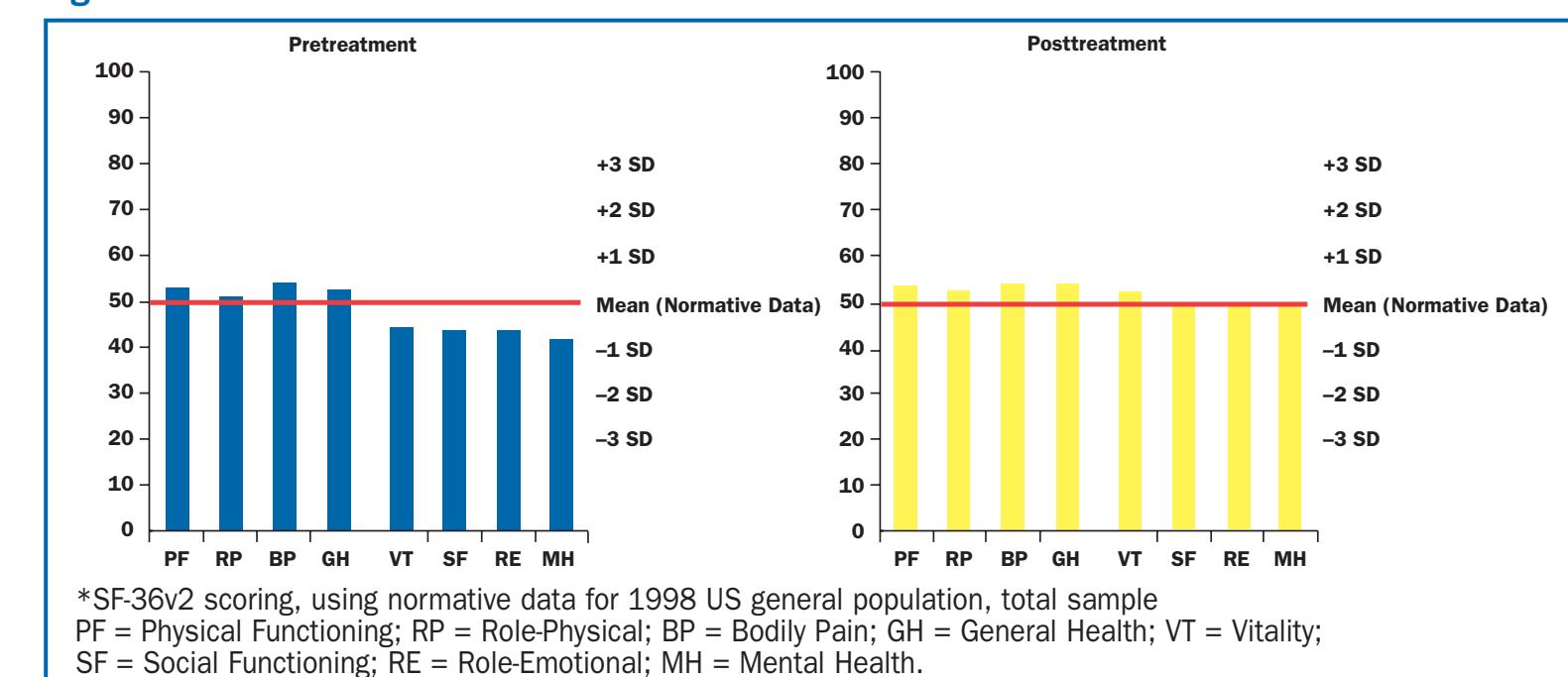


- Findings of the Medication Satisfaction Survey are summarized in Table 3.
- Most subjects reported overall satisfaction with MAS XR treatment.
- The majority of subjects reported being satisfied with once-daily dosing and ease of the medication regimen and most of them rarely skipped or missed a dose.

Tolerability and Safety

- Treatment-emergent AEs considered possibly related to MAS XR that were reported in ≥5% of subjects are summarized in Table 4.

Figure 8. SF-36v2 Norm-based Scores*



*SF-36v2 scoring, using normative data for 1998 US general population, total sample. PF = Physical Functioning; RP = Role-Physical; BP = Bodily Pain; GH = General Health; VT = Vitality; SF = Social Functioning; RE = Role-Emotional; MH = Mental Health.

Table 3. Medication Satisfaction Survey Results at End Point (ITT Cohort, N=702)

MSS Item	Strongly Agree/Agree, n (%)
Satisfied, overall	495 (70.6)
Dosing frequency (once daily)	621 (88.5)
Ease of medication regimen	646 (92.0)
Rarely skip/miss dose	606 (86.4)
Satisfied with behavior	474 (67.6)
Improved social interactions	360 (51.3)
Satisfied with ability to pay attention	473 (67.4)
Satisfied with duration of effect	454 (64.7)
Sleepy during the day	25 (3.6)
Difficulty falling asleep	85 (12.1)
Lessened appetite	296 (42.1)

Table 4. AEs Considered Possibly Related to MAS XR, Reported by ≥5% of Subjects

Adverse Event	No Previous Treatment (n=387) %	Previous Stimulant Treatment (n=281) %	Previous Nonstimulant Treatment (n=57) %	Total (N=725) %
Anorexia	7.8	2.8	3.5	5.5
Anxiety	6.5	4.6	7.0	5.8
Appetite decreased	21.2	14.6	28.1	19.2
Dizziness	5.2	3.2	1.8	4.1
Dry mouth	23.8	10.3	31.6	19.2
Fatigue	5.4	3.2	10.5	5.0
Feeling jittery	6.2	3.2	10.5	5.4
Headache	20.9	10.7	19.3	16.8
Heart rate increased	5.7	1.1	1.8	3.6
Insomnia	19.9	13.9	22.8	17.8
Initial insomnia	5.9	2.8	0.0	4.3
Irritability	8.0	2.8	7.0	5.9
Nausea	5.9	3.9	5.3	5.1
Tachycardia	2.3	1.4	5.3	2.2
Weight loss	9.8	11.0	19.3	11.0
Discontinuations because of adverse events	8.3	3.9	12.3	6.9

- The most common AEs contributing to study discontinuation during MAS XR treatment were increased heart rate (n=10; 1.4%), elevated blood pressure (n=6; 0.8%), and insomnia (n=6; 0.8%); all other AEs related to discontinuation were seen in ≤4 subjects each.
- At study end point, minimal changes in pulse (5.2 bpm), systolic blood pressure (0.9 mm Hg), and diastolic blood pressure (1.4 mm Hg) were observed; none of these changes was judged to be clinically significant.

CONCLUSIONS

- MAS XR at doses of up to 60 mg/d yields significant improvements in ADHD symptoms and QOL in adults with ADHD in a real-world community practice setting.
- Similar to previous findings, therapeutic benefits with MAS XR were maintained throughout the 10-week study period.
- The current findings further confirm that MAS XR therapy is well tolerated in otherwise healthy adult patients with ADHD.

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