Study Schema

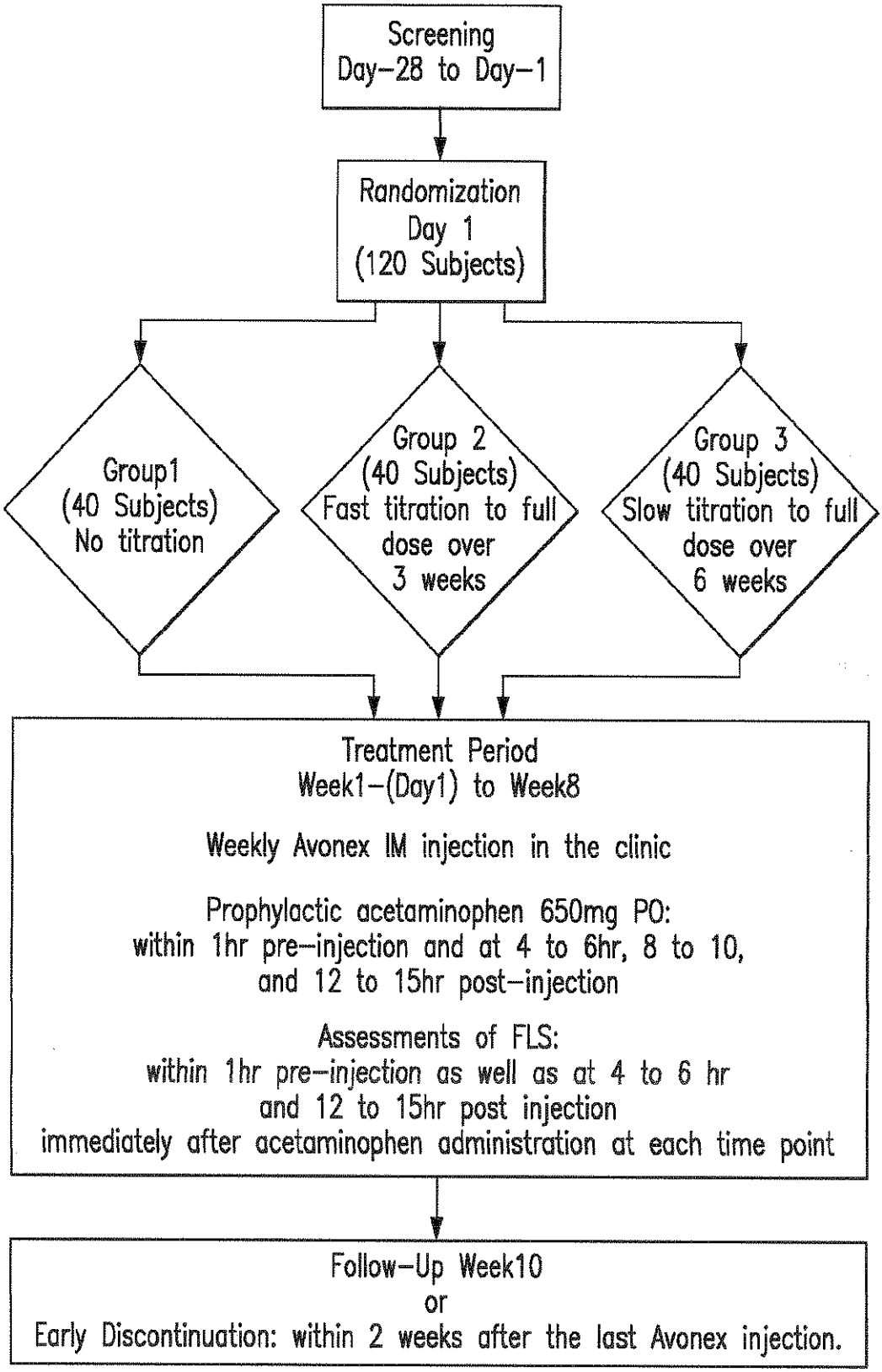


FIG. 1

Titration Schedules

Treatment Group	Titration Schedule	Doses of Weekly Avonex IM Injection							
		1	2	3	4	5	6	7	8
1	No titration	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg
2	Fast titration	Quarter dose 7.5 mcg	Half dose 15 mcg	Three Quarter dose 22.5 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg	Full dose 30 mcg
3	Slow titration	Quarter dose 7.5 mcg	Quarter dose 7.5 mcg	Half dose 15 mcg	Half dose 15 mcg	Three Quarter dose 22.5 mcg	Three Quarter dose 22.5 mcg	Full dose 30 mcg	Full dose 30 mcg
All Groups	Prophylactic Medication: At each dosing visit, acetaminophen 650mg PO will be given within 1 hour prior to the Avonex injection, and at 4 to 6 hours, 8 to 10 hours, and 12 to 15 hours after the injection.								

FIG. 2

Primary Endpoint: FLS score

- Each symptom (muscle aches, chills, and fatigue) assigned a score from 0 to 3 by the Investigator as follows:
  - 0 = Absent
  - 1 = Mild, did not interfere with daily activities
  - 2 = Moderate, sufficient to interfere with daily activities
  - 3 = Severe, bed rest required
- Body temperature will be recorded to determine presence of fever using the following scale:
  - 0 (<99.1°F)
  - 1 (≥99.1 but <100.1°F)
  - 2 (≥100.1 but <101.1°F)
  - 3 (≥101.1°F)
- Total FLS assessment scoring
  - The total score (sum of the 3 symptom scores and the fever score) for each of the 3 timepoints (pre-injection, 4 to 6 hours, and 12 to 15 hours) calculated during data analysis.
  - A total score of 2 points or greater above the pre-injection score will be considered to be positive for presence of FLS.

FIG. 3

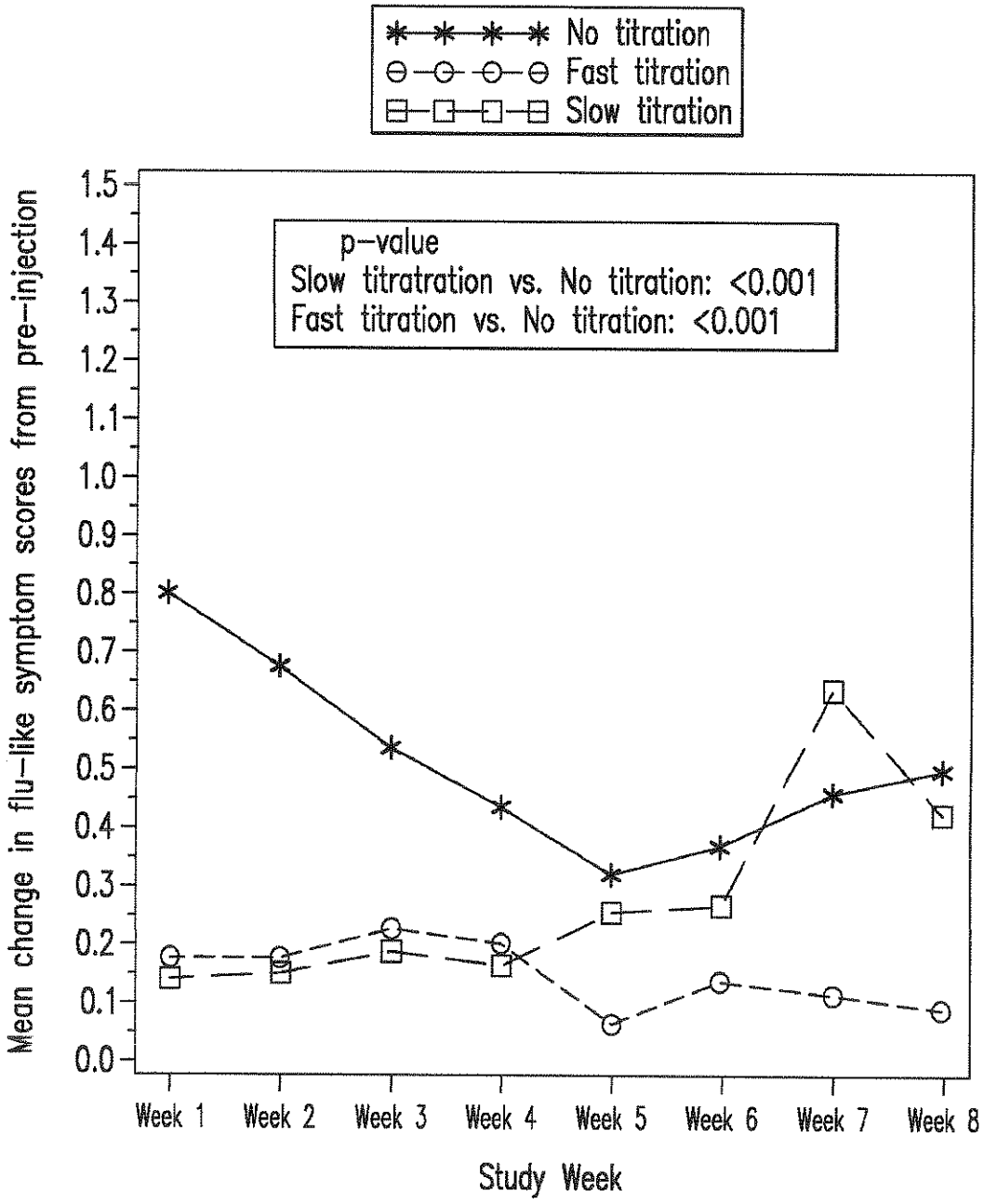

Primary Outcome Variable: Change in total FLS score from pre-injection to 4 to 6 hours after injection over 8 weeks
No titration
Fast titration
Slow titration
p-value
Slow titratration vs. No titration: <0.001
Fast titration vs. No titration: <0.001
Mean change in flu-like symptom scores from pre-injection
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Study Week

FIG.4

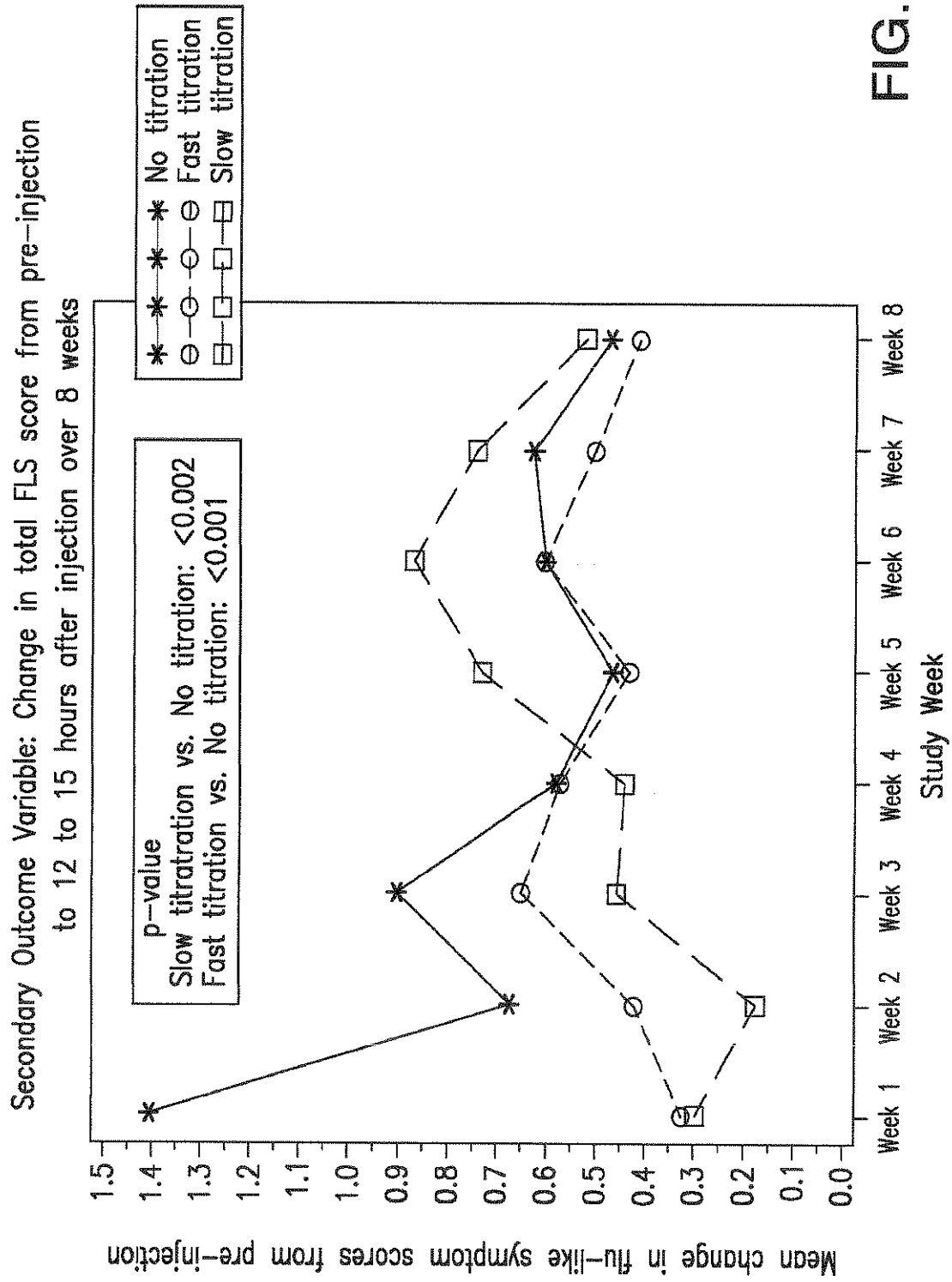

Secondary Outcome Variable: Change in total FLS score from pre-injection to 12 to 15 hours after injection over 8 weeks
p-value
Slow titratration vs. No titration: <0.002
Fast titration vs. No titration: <0.001
No titration
Fast titration
Slow titration
Mean change in flu-like symptom scores from pre-injection
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6
Week 7
Week 8
Study Week

FIG.5

Secondary Outcome Variable: The incidence of FLS (Δ score ≥ 2) at 4 to 6 hours and at 12 to 15 hours after injection over 8 weeks

Odds ratio of incidence of flu-like symptoms (total score >=2 over pre-injection) over 8 weeks – LOCF analysis

	No titration	Fast titration	Slow titration
Number of subjects dosed	78 (100)	78 (100)	78 (100)
Time A (4 to 6 hours post-injection)			
Odds ratio [95% CI)		0.179 [0.075, 0.429]	0.414 [0.194, 0.884]
p-value (a)		<0.001	0.023
Time B (12 to 15 hours post-injection)			
Odds ratio [95% CI]		0.469 [0.272, 0.807]	0.562 [0.338, 0.936]
p-value (a)		0.006	0.027

NOTE 1: Numbers in parentheses are percentages.
2: Missing values were imputed using last observation carried forward (LOCF).
(a) Odds ratio [95% CI] and p-value were from Generalized Estimating Equations method analyzing the overall treatment difference on the repeated measures over 8 weeks. The odds ratio was estimated using No titration group as the control group.

FIG.6

SUBSTITUTE SHEET (RULE 26)

	No titration	Fast titration	Slow titration
Number of subjects dosed	78 (100)	78 (100)	78 (100)
Time A (4 to 6 hours post-injection)			
LS means	0.539 [0.425, 0.652]	0.132 (0.018, 0.245]	0.267 [0.153, 0.380]
Diffirence of LS means [95% CI]		−0.407 [−0.566, −0.248]	−0.272 (−0.431, −0.113]
p-value (a)		<0.001	<0.001
Time B (12 to 15 hours post-injection)			
LS means	0.753 [0.645, 0.861]	0.475 [0.367, 0.583]	0.515 (0.407, 0.623)
Difference of LS means [95% CI]		−0.278 [−0.430, −0.126]	−0.238 (−0.390, −0.086]
p-value (a)		<0.001	0.002

NOTE 1: Numbers in parentheses are percentages.
2: Missing values were imputed using last observation carried forward (LOCF).
(a) LS means [95% CI] and p-value were from Mixed model analyzing the overall treatment difference on the repeated measures over 8 weeks. The difference of LS means was estimated using No titration group as the control group.

FIG.7

SUBSTITUTE SHEET (RULE 26)

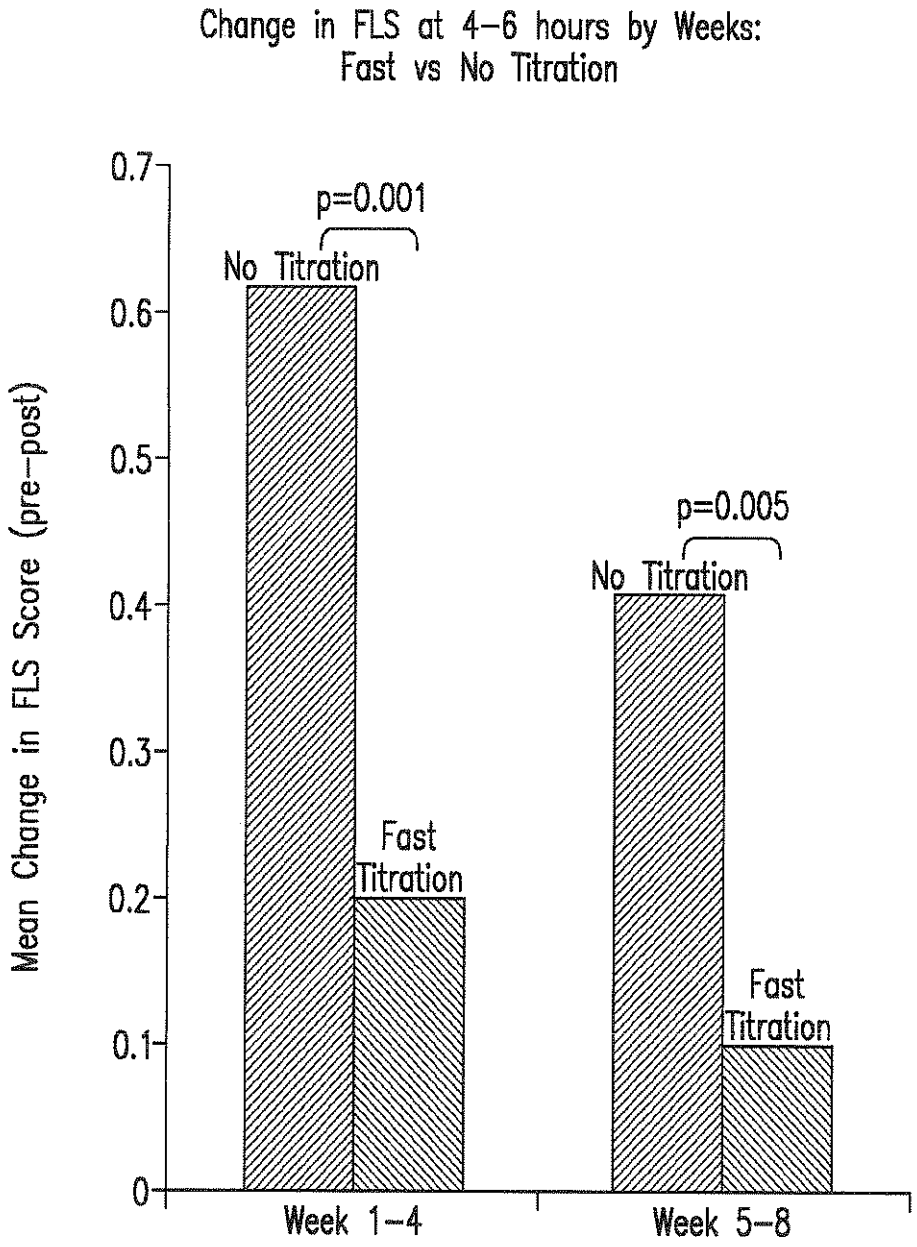

Change in FLS at 4–6 hours by Weeks:
Fast vs No Titration
Mean Change in FLS Score (pre–post)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
p=0.001
No Titration
Fast
Titration
p=0.005
No Titration
Fast
Titration
Week 1–4
Week 5–8

FIG.8

Change in FLS at 4–6 Hours by Weeks

	No Titration	No Titration
Number of subjects dosed	78 (100)	78 (100)
Week 1 – 2		
n	78	78
Mean	0.74	0.15
SD	1.127	0.303
Median	0.50	0.00
Min, Max	0.0, 7.0	0.0, 1.5
p–value (a)		<0.001
Week 3 – 4		
n	78	78
Mean	0.49	0.18
SD	1.013	0.386
Median	0.00	0.00
Min, Max	0.0, 7.0	0.0, 2.0
p–value (a)		0.012

NOTE 1: Numbers in parentheses are percentages.
2: Missing values were imputed using last observation carried forward (LOCF).
(a) p–value from ANOVA.

FIG.9