Cardiac Toxicity in Chronic Fatigue Syndrome: Results from a Randomized 40-Week Multicenter Double-blind Placebo Control Trial of Rintatolimod

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ABSTRACT

The sedentary life-style caused by extreme fatigue is a significant risk factor for heart disease which is a leading cause of death in Chronic Fatigue Syndrome (CFS) patients. AMP-516, a 40-week double-blind, placebo-controlled study in CFS patients to evaluate the effectiveness of rintatolimod (Ampligen®) included repeated QT interval measurements. A ≥5 ms post-treatment mean increase in QT prolongation was observed in the placebo group, while a <5 ms mean post-treatment increase in QT prolongation was observed in the rintatolimod patients. A greater proportion of the placebo patients were found to have significant QT prolongation, compared to patients receiving rintatolimod. The increase in QT in the placebo group was associated with continued use of concomitant medications known to prolong QT; patients randomized to receive rintatolimod were able to significantly reduce their dependence on these same medications. Reducing the risk of cardiac toxicity by reducing fatigue and the use of concomitant medications with serious side effects is an important clinical objective and underscores the seriousness of CFS.

INTRODUCTION

Chronic Fatigue Syndrome (CFS) is a severe disorder consisting of profound fatigue and a variety of other debilitating symptoms that affects up to 4 million Americans[1, 2]. Heart failure is a major cause of death with CFS, even in the female population where the age of disease onset is typically 38-42 years of age[3]. Currently, there are no approved treatments for this disease, and severely afflicted patients often become sedentary and bedridden. To evaluate the investigational drug rintatolimod (a TLR3 agonist, which modulates innate and adoptive immunity) for CFS, Study AMP-516 was conducted as a 40-week double-blind, randomized, multicenter, placebo-controlled trial (n=234)[4]. Table 1 contains a summary of the patients enrolled and treated in AMP-516. The mean duration of symptoms of CFS was 9.64

Table 1: *Summary of Onset History and Duration of CFS Symptoms (AMP-516)*

Parameter	Rintatolimod (n=117)	Placebo (n=117)	All (n=234)
Age at onset, years			
n	117	117	234
Mean (sd)	34.0 (9.33)	34.1 (9.83)	34.0 (9.56)
Median	33.0	34.0	33.0
Range	11 to 54	12 to 53	11 to 54
Duration of symptoms of chronic fatigue syndrome, years			
n	117	117	234
Mean (sd)	**9.56 (5.36)**	**9.73 (6.08)**	**9.64 (5.72)**
Median	8.30	8.90	8.50
Range	1.4 to 24.3	1.4 to 35.6	1.4 to 35.6
Time from diagnosis of chronic fatigue syndrome, years			
n	117	117	234
Mean (sd)	5.93 (3.56)	5.90 (3.66)	5.92 (3.60)
Median	5.10	5.50	5.30
Range	0.3 to 14.9	0.4 to 14.6	0.3 to 14.9

sd=Standard deviation.

years, and patients had been suffering with CFS for over 5 years prior to enrollment.

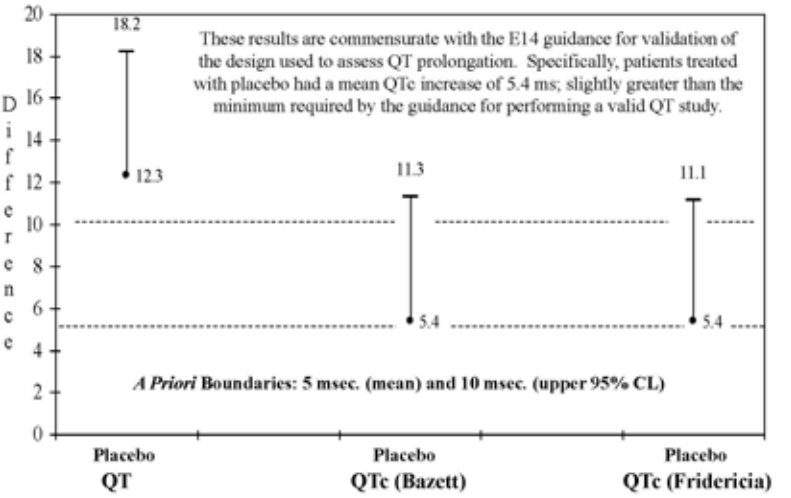
The profound inability of CFS patients to exercise and the chronic duration of their sedentary life-style is a significant risk factor for heart disease. Heart failure is a leading cause of death in patients with CFS[3]. Over 20% of the total deaths of CFS subjects investigated by Jason, et al. were secondary to heart failure, which is known to induce QT prolongation most likely through upregulation of KCNE1[5]. For patients with CFS, more than twice as many women die from heart failure compared to men.

MATERIALS AND METHODS

A comprehensive analysis of QT interval assessments including the QTc interval was performed in AMP-516 per ICH E14 Guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Anti-arrhythmic Drugs (October 2005, ICH). In AMP-516, the Safety Population evaluated for QT prolongation consisted of 190 subjects (91 received rintatolimod (Poly I : Poly $C_{12}U$) and 99 placebo) with a baseline and post-baseline QT interval determination performed under standardized conditions. The clinical ECG database consisted of over 1,000 12-lead surface ECGs obtained during baseline (twice) and at weeks 20, 34, and 40. All ECGs were obtained by an experienced team headed by an exercise physiologist. The team traveled to each site and obtained the ECGs prior to administering the treadmill tolerance test. The same ECG analysis equipment (Pulse Biomedical, Inc., Norristown, Pennsylvania USA) was utilized for all subjects at all study sites throughout the duration of the AMP-516 study.

Data was recorded and differences in proportions were analyzed using a 2-tailed Fisher's exact test. Intra-arm differences from baseline in continuous parameters were analyzed using a paired-difference t-test.

***Figure 1**: QT Prolongation Observed in the Placebo Group, Based on the Upper One-Sided 95% Confidence Limits from the Intra-Patient Mean Differences from Baseline QT (milliseconds) Values.*



Probability values < 0.05 were considered to be significant; values <0.1 but ≥ 0.05 were considered highly suggestive of a significant difference. All statistical tests were performed using the SAS System (Cary, NC).

RESULTS

There was no significant difference in the mean QT values recorded at baseline, based on the actual recorded values, or the corrected values using either the Bazett's or Fridericia's formula. The differences at baseline between the placebo and rintatolimod randomized treatment groups (rintatolimod – placebo) was -6.4, -3.0, and -4.2 for QT, Bazett's, and Fridericia, respectively. Although suggestive of higher measurements in the placebo group, none of the differences were significant at the alpha = 0.05 level.

The intra-patient average QTc (Bazzet) baseline values were examined relative to the E14 guidance using the categorical classification of QTc values. Based on the lowest threshold value (>450 msec), over 8% of the patients in the QTc analysis had an average baseline QTc value of >450 msec (95% CI: 4.9% to 13.3%). This finding suggests that a recognizable population of CFS patients who participated in AMP-516 were at increased risk of cardiovascular disease and cardiac-related events.

The QTc values from the placebo group from AMP-516 were analyzed to determine the mean QTc interval based on the intra-patient changes from baseline (ref. Figure 1). These results are commensurate with the E14 guidance for validation of the design used to assess QT prolongation. Specifically, patients treated with placebo had a mean QTc increase of 5.4 ms; slightly greater than the minimum required by the guidance for performing a valid QT study.

The maximum on-study QTc interval (QTcB) was determined for each patient and categorized using the cutoff points specified in the E14 Guidance Document, QTc intervals > 500, > 480, and > 450 msec. In general, there were more placebo patients over the respective thresholds, compared to patients randomized to receive rintatolimod. The post-baseline results for the QT values, observed and corrected are presented in Figure 2. Patients randomized to receive placebo had a significantly longer QT interval, compared to patients randomized to receive rintatolimod (p=0.049). Although

Figure 2: *No Evidence of Increased QT Prolongation with Rintatolimod Compared to Placebo, Based on the Upper One-Sided 95% Confidence Limits from the Intra-Patient Mean Differences in QT (milliseconds) Values by Randomized Treatment Assignment*

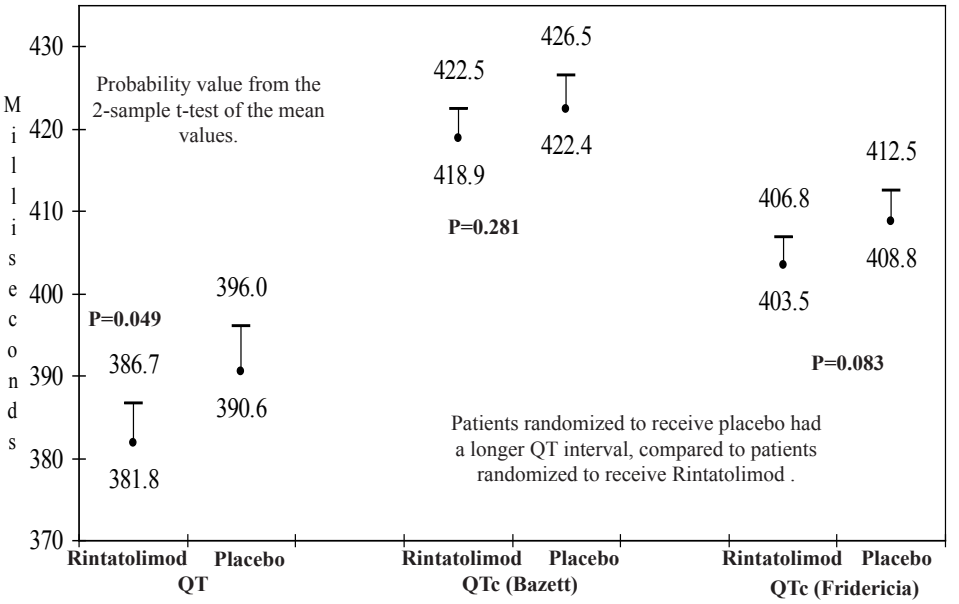


Figure 3: *No Evidence of Increased QT Prolongation with Rintatolimod Compared to Placebo, Based on the Upper One-Sided 95% Confidence Limits from the Intra-Patient Mean Differences in QT (milliseconds) Values by Randomized Treatment Assignment*

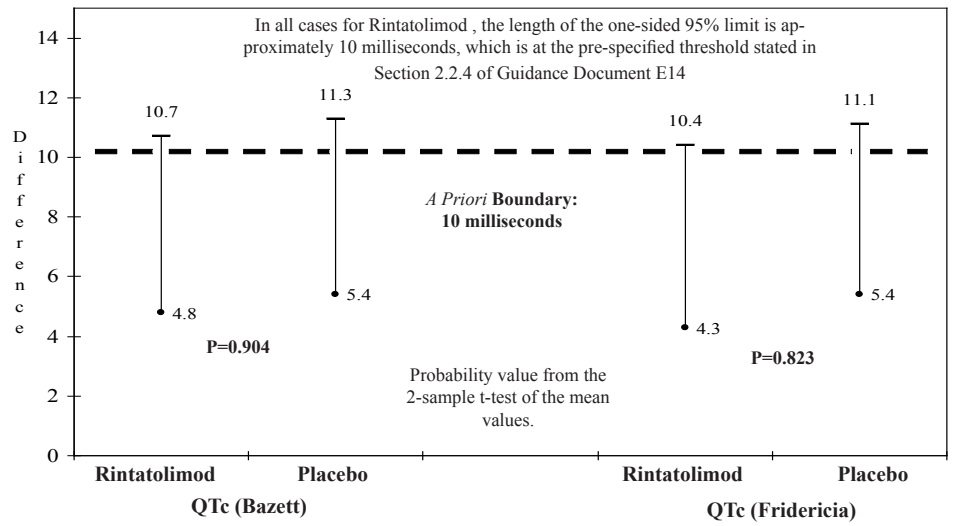


Figure 4: *Mean (95% CI) of the Intra-Patient Differences in QT (milliseconds) Values Between Placebo Patients Who Either Did or Did Not Received Concomitant Medications Known to Prolonged the QT Interval*

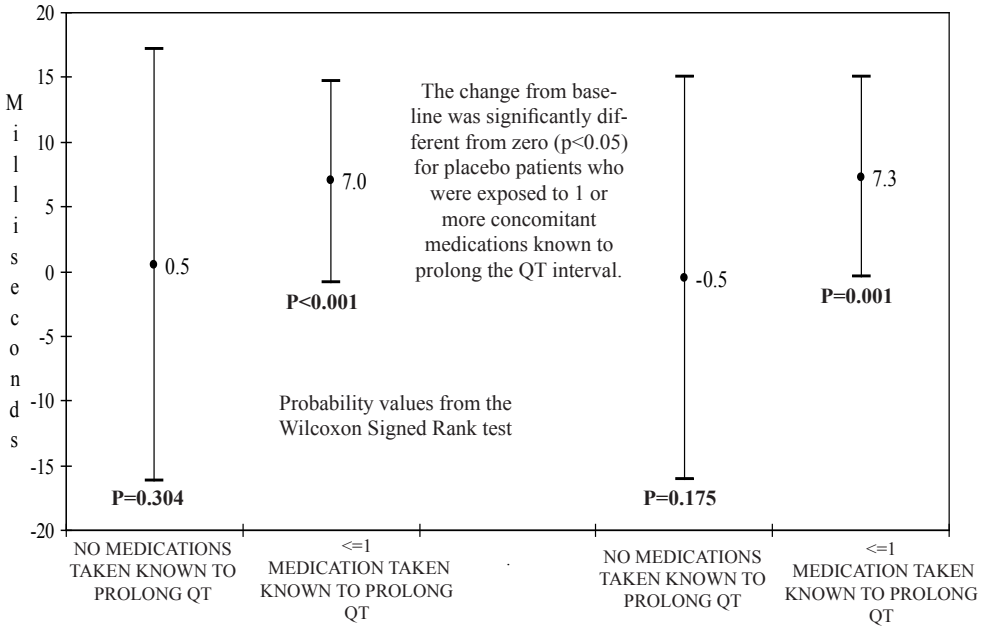


Figure 5*: Arithmetic Average QTc (Bazett) from Placebo Patients Who Received 0, 1, and 2 or More Different Concomitant Medications Known to Prolong QT by Randomized Treatment Assignment*

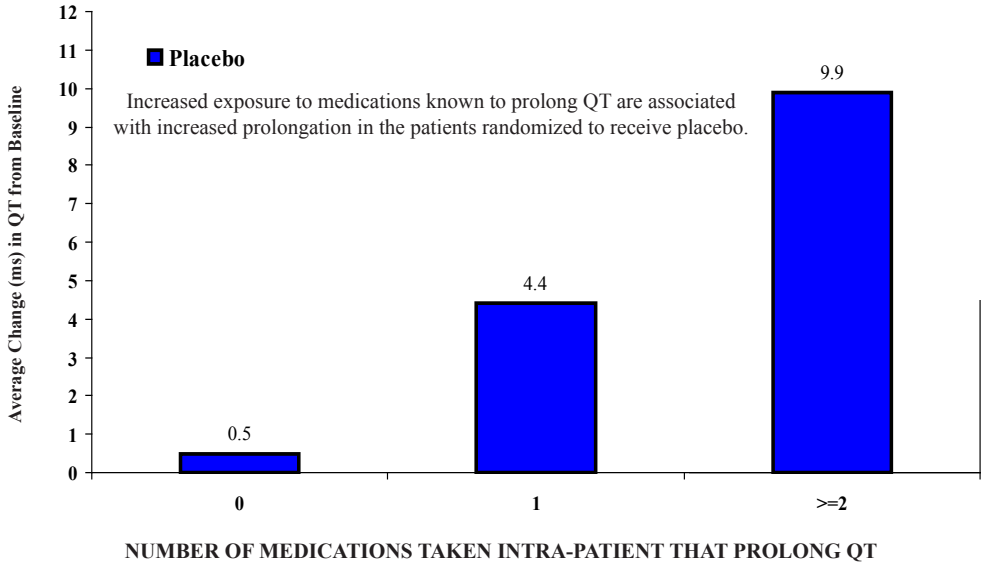
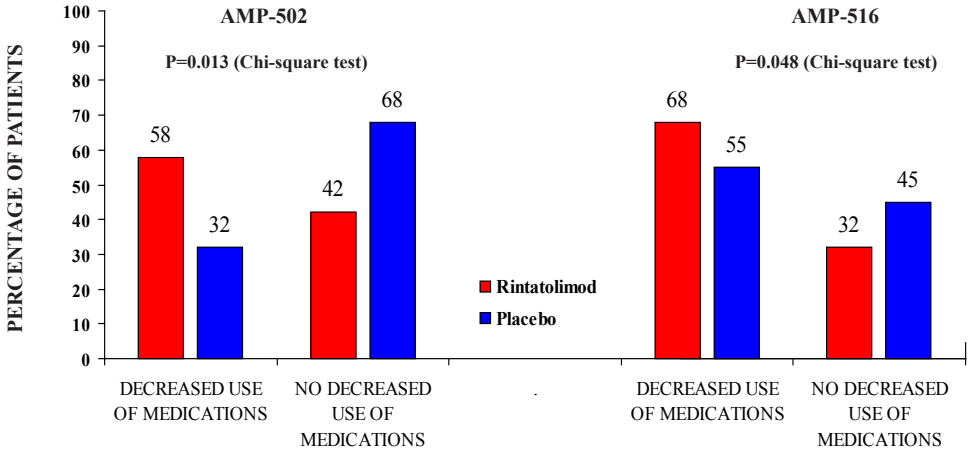


Figure 6: Percentage of Patients Who had a Decrease in the Number of Days of Exposure to Medications Known to Prolong QT by Study and Randomized Treatment Assignment



trending in the same direction, the corrected QT values were not significantly different at the alpha = 0.05 level between patients randomized to receive either placebo or rintatolimod.

QT Results Based on the Change from Baseline

Patients randomized to receive placebo had a slightly longer QT interval, compared to patients randomized to receive rintatolimod, however the difference was not significant at the alpha = 0.05 level. Based on these results, there is no evidence that patients treated with rintatolimod are at an increased risk of cardio-toxicity. The intra-patient post-baseline minus baseline results for the QT values, observed and corrected are presented graphically in Figure 3.

The length of the one-sided 95% confidence limit from the arithmetic average, based on the intra-patient differences, is presented in Figure 4. For patients randomized to receive rintatolimod, the length of the one-sided 95% limit is approximately 10 milliseconds, equal to the pre-specified threshold stated in Section 2.2.4 of Guidance Document E14. The corrected QT prolongation data from the rintatolimod treatment group does not exclude 10 ms, however the upper one-sided 95% confidence limit is less than observed in the placebo arm. Additionally, the mean change from baseline in the rintatolimod treatment group is less than 5 ms, while the mean change observed in the placebo group exceeds 5 ms.

Many of the concomitant medications utilized by the CFS subjects are known to prolong the QT interval or induce Torsades de Pointes (TdP). No drugs are currently approved for the treatment of CFS. Accordingly, CFS patients utilize numerous concomitant medications in a largely unsuccessful effort to relieve the chronically debilitating symptoms of CFS. Because of the importance of studying the potential proarrhythmic effect of rintatolimod in the actual population being chronically exposed to this vast array of concomitant medications including many known to prolong the QT interval, a QT study conducted per the E14 Guidance in a CFS population is substantially superior to a QT study conducted in a normal healthy volunteer population. The cumulative exposure to rintatolimod over 40 weeks in this severely debilitated population taking an array of QT interval prolonging drugs can not be replicated in a normal healthy population. The use of concomitant medications in AMP-516 was permitted to treat the symptoms and morbidity associated

with CFS.

Although approved for general use, several of the concomitant medications have an associated product warning that exposure to the medication may cause QT prolongation, translating to an increased risk of cardio toxicity. Within the placebo group, the change from baseline was not significantly different from zero for patients who were not exposed to concomitant medications known to prolong the QT interval. However, the change from baseline was significantly different from zero ($p<0.05$) for placebo patients who were exposed to 1 or more concomitant medications known to prolong the QT interval. Figure 5 provides a graphical depiction of the increased QT intervals in the placebo patients taking 0, 1, and ≥2 medications with a known risk for prolonging QT.

An additional analysis was performed to determine if patients randomized to receive rintatolimod experienced a significant reduction in the cumulative exposure to medications that prolong QT, compared to patients randomized to receive placebo. Sixty-eight of the 100 patients (68.0%) randomized to receive rintatolimod experienced a reduction in exposure to concomitant medications with a known risk of prolonging QT, compared to 59 of the 108 patients (54.6%) randomized to receive placebo. Comparing the proportion of patients between randomized treatment assignment and decreased exposure revealed a significant difference in favor of rintatolimod ($p=0.048$). Patients randomized to receive rintatolimod were one and three-quarters times more likely to have reduced exposure to medications known to prolong QT, compared to placebo (Odds ratio: 1.76 [95% CI: 1.00 to 3.11] ref. Figure 6).

These findings were also found in an earlier double-blind, randomized, placebo controlled study (AMP-502) of 92 CFS patients[6]. Twenty-six of the 45 patients (57.8%) randomized to receive rintatolimod experienced a reduction in exposure to concomitant medications with a known risk of prolonging QT, compared to 15 of the 47 patients (31.9%) randomized to receive placebo. Comparing the proportion of patients between randomized treatment assignment and decreased exposure revealed a significant difference in favor of rintatolimod ($p=0.013$). Patients randomized to receive rintatolimod were approximately 3 times more likely to have reduced exposure to medications known to prolong QT, compared to patients randomized to receive placebo (Odds ratio: 2.92 [95% CI: 1.25 to 6.84]).

CONCLUSION

The QT interval prolongation results from the AMP-516 study provide a head-to-head comparison between patients randomized to receive either rintatolimod or placebo. The increase in QT prolongation observed in the placebo group provides concurrent validation of the design, given a ≥5 ms post-treatment increase was observed in the placebo group of CFS patients. The increase observed in the placebo patients can be directly attributable to the use of concomitant medications known to prolong QT, coupled with a sedentary life-style known to be a risk factor for heart disease.

Increased stamina and tolerance to exercise are important factors in reducing the cardiovascular risk associated with CFS. In both AMP-502 and AMP-516, rintatolimod resulted in a statistically significant ($p<0.05$) increase in mobility and stamina (exercise tolerance). Reducing the sedentary influence of CFS through increased stamina, coupled with the reduced dependence on medications that can prolong QT, is an important step in the management of this chronic disease. The analysis of the intra-patient QT interval data from AMP-516, where over 1,000 EKGs were recorded during the course of the study revealed evidence of an increased risk of pro-arrhythmic potential in the placebo group, compared to the rintatolimod treated group. Given more patients in the placebo group continue with their use of medications, compared to patients receiving rintatolimod, it is indeterminate as to the exact contribu-

tion the increase in exercise tolerance had on abrogating QT prolongation in the rintatolimod group. Regardless, based on the thresholds published in the FDA guidelines for all new drugs, there were significantly more intra-patient measurements in placebo patients that were prolonged, compared to the rintatolimod treated patients.

Rintatolimod treatment allowed CFS subjects to reduce their dependence on concomitant medications used to treat debilitating symptoms of CFS, coincidentally reducing exposure to drugs known to prolong the QT interval. This may suggest a new therapeutic strategy to potentially mitigate the incidence of heart failure/sudden death in this relatively young, predominantly female, population by reducing their dependency on palliative medications associated with increased risk of TdP/sudden death. Further clinical studies should provide more insight into the potential relationship between polypharmacy (as practiced in alleviating CFS symptomatology), QT interval prolongation, and the relative incidence of catastrophic cardiovascular events in this population.

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