-Tracked Safety Issue (TSI) Integrated Review Memorandum

Division of Psychiatry Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDA/BLA	*207318*
Drug name	*Nuplazid (pimavanserin)*
TSI #	*1890*
TSI open (create) date	*6 April 2018*
Safety Issue Name	*Mortality, Autonomic dysfunction (blood pressure lability), falls and insomnia*
Author name	*Marc Stone, M.D.*
Date	*17 August 2018*

I. OVERALL ASSESSMENT AND RECOMMENDATION(S)

The current Nuplazid label contains a boxed warning that the use of antipsychotic drugs in elderly patients with dementia is associated with approximately 70% increase in mortality. Our review found that:

1. The population of patients with Parkinson's disease psychosis is mostly elderly and very ill. The annual mortality rate in population-based observational studies is 25-30%. An annual mortality rate of up to 60% among patients taking Nuplazid would be would be consistent with the boxed warning.
2. The large number of reported deaths in Nuplazid patients is a consequence of both the high mortality rate in this population and a high reporting rate due to distribution of most of the drug through specialty pharmacies and other channels where patient use was closely monitored. If the reporting rate from the specialty pharmacy channel were as low as it was from other channels, the overall mortality reporting rate would be 88% lower.
3. A review of 893 case reports of deaths in patients taking pimavanserin did not identify any new safety findings with pimavanserin, compared to the premarketing safety profile
4. Because of the use of specialty pharmacies and distributor, we were able to identify a representative sample of pimavanserin patients with important information such as age and sex and how long the drug was taken. Our analysis of this data showed that the rate and pattern of discontinuation was much like that seen in clinical trials.
5. Beyond the first two months of use, the annualized rate of discontinuation was 50%. Even under the extreme assumption that all these discontinuations were due to deaths, this mortality rate would be consistent with the boxed warning.

6. The reporting rate of deaths relative to the total number of patients taking pimavanserin changes little with length of exposure. If pimavanserin were causing a significant number of deaths, those deaths would be more likely to occur and to be reported within the first few weeks or months of use.
7. Review of all the Sponsor's clinical studies did not show any effect on postural changes in heart rate or blood pressure in elderly subjects for dosages within the therapeutic range. Effects at supratherapeutic dosages were slight for heart rate and not observed for blood pressure.
8. Our review of cases showed concomitant use of pimavanserin with other antipsychotic drugs to occur not infrequently. We know of no evidence for clinical improvement in symptoms of Parkinson's Disease psychosis when pimavanserin is combined with other antipsychotic drugs and there is reason to believe that the incidence of adverse events, particularly death, would be increased. Much of the concomitant use, however, appears to be low dosages of quetiapine used off-label as a sleep aid. Such dosages likely have little incremental effect on either risk or benefit.

II. BACKGROUND

Pimavanserin was approved in April 2016 for the treatment of hallucinations and delusions associated with psychosis in end-stage Parkinson's disease (PDP). In randomized placebo-controlled clinical trials, the incidence of serious adverse events was 7.9% with pimavanserin and 3.5% with placebo. No individual type of adverse event predominated and there appeared to be no unifying pathological mechanism or premonitory signal. Deaths occurred in four of 383 (1%) subjects assigned to pimavanserin and one of 231 (0.4%) of those assigned to placebo. Prior experience with the use of antipsychotic drugs in similar populations of elderly patients with dementia showed a similar excess of deaths with active drug treatment compared to placebo with no predominant cause of death. Although, by itself, the evidence for increased mortality with pimavanserin was not statistically significant and lacked evidence for a mechanism, the similarity to the elevated mortality observed with the use of other antipsychotic drugs to treat dementia prompted the addition of the same boxed warning for increased mortality that appears in the labeling for all antipsychotic drugs. Pimavanserin was also found to have QT effects in the range not generally considered to be clinically significant by itself but could potentially increase risk if combined with drugs that have more substantial QT effects.

This TSI was prompted by media reports that pointed to large numbers of adverse event reports, particularly deaths, with pimavanserin.

III. SIGNIFICANT REVIEW FINDINGS

1. *The population of patients with Parkinson's disease psychosis is mostly elderly and very ill. The annual mortality rate in population-based observational studies is 25-30%. An annual mortality rate of up to 60% among patients taking*

Nuplazid would be would be consistent with the boxed warning.

The OSE review identified several observational studies that estimated the mortality rate for Parkinson's Disease and related psychosis or dementia. In one study[1], the six-year mortality rate for Medicare beneficiaries with an incident diagnosis of Parkinson's Disease age 67 and older was 64.4%. For Parkinson's patients with dementia it was 71.9%. According to Social Security Administration life tables for the same period as the study (2002-2008), the death rate for the entire Medicare population age 67 and older was 31.5%. This translates to annual mortality rates of 15.8% for Parkinson's Disease, 19.1% for Parkinson's Disease with dementia and 6.1% for the general age-matched population. This represented a hazard ratio of 2.73 for Parkinson's Disease relative to the general population and 3.36 for Parkinson's patients with dementia. The hazard ratio for dementia relative to no dementia for Parkinson's patients was 1.72, indicating a hazard ratio of 1.95 for Parkinson's Disease without dementia. The average age of Parkinson's patients in this population was about 80 and the prevalence of dementia was 69.6%.

In the context of Parkinson's disease, psychosis may have an even poorer prognosis than dementia. The two conditions appear to be clinically distinguishable: a prospective observational study[2] in a somewhat younger population (average age 65) found 53% of patients with Parkinson's disease psychosis to be demented compared to 15% of Parkinson's patients without psychosis. A more recent study[3] of the Medicare population (2012-2015) by the authors of the earlier Medicare study identified Parkinson's patients by the presence or absence of psychosis found age-standardized mortality in the cohort with psychosis was significantly higher than in the cohort without dementia (28.2 vs 7.3 deaths per 100 patient-years; a hazard ratio of 4.4). The average age for the combined cohorts was 80, as in their previous study. In the general population, the average annual mortality rate at age 80 is 5.0%. Hence the hazard ratio for Parkinson's-related psychosis relative to the general population is about 6.4.

In clinical studies, subjects were younger on average than those with PDP in the Medicare population with an average age of 71 (Table 1):

Table 1: Observed Mortality in Nuplazid Phase 2/3 Studies

Study	Number of Subjects	Average Age	Patient-years of Observation	Expected Deaths*	Observed Deaths
006	60	70.9	9.4	0.25 (1.60)	0
010**	39	72.4	70.9	2.23 (14.3)	8
012	298	69.3	31.6	0.74 (4.75)	2
014	123	72.1	26.1	0.76 (4.91)	0
015**	459	72	749	22.2 (142.9)	43
020	198	72.7	36.9	1.11 (7.15)	3
Total	NA***	71.4	909.1	27.3 (175.6)	56

*For age- and sex-matched general population and (population with PDP)
**Uncontrolled open-label studies
***Not Applicable because of rollover from double-blind into open-label studies

The observed annual mortality rate for all subjects (drug or placebo) with PDP in the Nuplazid development program was 6.2%. This is approximately twice what would have been expected in the age- and sex-matched general population (3.0%). It is also less than a third of what would have been expected (19.3%) for typical PDP patients with the same age and sex distribution (based upon a hazard ratio of 6.4), probably reflecting selection of patients with fewer comorbid health issues for inclusion in the clinical trial.

Because Nuplazid is mostly distributed through specialty pharmacies, the Sponsor was able to provide information on the age and sex distribution of patients. Applying this information to contemporary life tables, the expected annual mortality rate for the age- and sex-matched general population is 4.7% (the average age is 76 years). Applying a hazard ratio of 6.4, the expected annual mortality rate for this population of patients receiving pimavanserin treatment can be estimated to be 27%. In the FDA analysis of randomized placebo-controlled trials of antipsychotic drugs in dementia, the incidence of death was 1.7 (95% confidence interval 1.2 to 2.4) times higher in subjects who received active drug compared to placebo; the Nuplazid label assumes the same risk applies to patients in the PDP population. Applying this risk to the expected 27% mortality risk in the population would mean that an annual mortality rate of 46% with a 95% confidence range of 32% to 65% would be consistent with current labeling.

2. *The large number of reported deaths in Nuplazid patients is a consequence of both the high mortality rate in this population and a high reporting rate due to distribution of most of the drug through specialty pharmacies and other channels where patient use was closely monitored. If the reporting rate from the specialty pharmacy channel were as low as it was from other channels, the overall mortality reporting rate would be 88% lower.*

The Sponsor has reported (b) (4) patient-years of exposure to pimavanserin among distribution channels where unique patients were known (assuming all distributed product was consumed). This represents only (b) (4)% of all product distributed but 843 (95.2%) of the 885 deaths reported to the Sponsor between product launch on 31 May 2016 and 28 February 2018. (The OSE Summary Review interpreted the Sponsor's initial response as meaning that 85% of deaths were reported through these distribution channels; subsequent clarification by the Sponsor led to the 95.2% figure.) The death reporting rate through these channels calculates to be 13.6 deaths reported per 100 patient-years of exposure. Forty-two deaths were reported through other channels with about (b) (4) patient-years of exposure, a rate of 1.05 deaths per 100 patient-years. This means that the reporting rate for the specialty pharmacy distribution channel was 13 times higher than from other sources. If the reporting rate from the specialty pharmacy channel were as low as it was from other channels, the total number of reported deaths would be 88% lower, 107 rather than 885.

3. *A review of 893 case reports of deaths in patients taking pimavanserin did not identify any new safety findings with pimavanserin, compared to the premarketing safety profile.*

   These findings are covered in detail in the OSE Integrated Review. Most solicited cases provided insufficient information to assess drug-event causality, which may be a consequence of routine reporting by specialty pharmacies of deaths in patients even when there were no concerns about a role for pimavanserin in the death.

4. *Because of the use of specialty pharmacies and distributor, we were able to identify a representative sample of pimavanserin patients with important information such as age and sex and how long the drug was taken. Our analysis of this data showed that the rate and pattern of discontinuation was much like that seen in clinical trials. The most notable difference was a higher discontinuation rate during the second month of treatment among the post-approval treatment population compared to the development program*

   In the clinical development program there were six phase 2 and 3 studies (four randomized placebo-controlled and two open label extension). with 621 subjects exposed to pimavanserin. Because all subjects were eligible in principle to enter open-label studies 010 or 015, the decision to discontinue pimavanserin within the first few years of study was made by patients, their guardians and their physicians rather than imposed by study termination rules. Reasons for discontinuation of pimavanserin in the clinical development program would, except for drug cost, be comparable to those in the post-marketing period. There were 621 subjects exposed to pimavanserin in phase 2 and 3 with exposure totaling 851 subject-years. Because of the specialty distribution program, the sponsor was able to identify (b) (4) unique patients who have been prescribed pimavanserin by length of use and whether they are currently receiving the drug. These patients collectively have had approximately (b) (4) patient-years of exposure. Figure 1 compares discontinuation rates by month of exposure for the development program with those seen post-marketing.

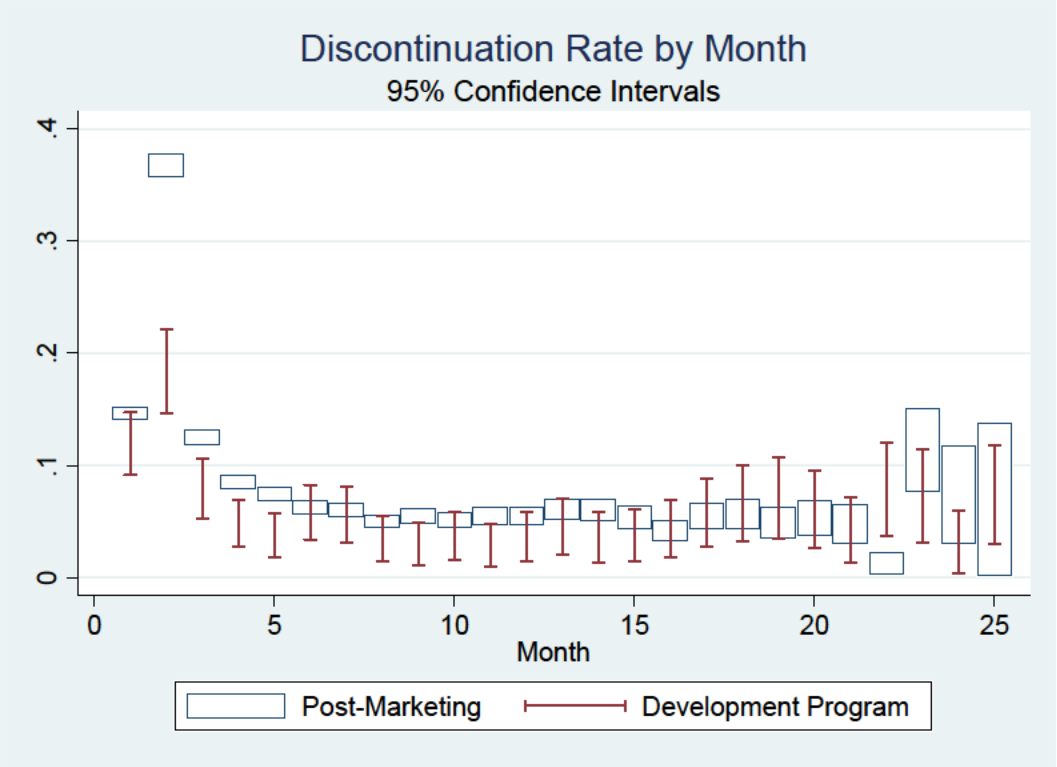


Figure 1: Discontinuation rates by months of exposure to pimavanserin

During the first five months of exposure, the discontinuation rate was higher post-marketing than during the development program but only notably so during the second month of use; subsequent discontinuation rates are indistinguishable between the two groups. There are several possible explanations. The most concerning would be a higher rate of death or non-fatal serious adverse reactions due to the drug. It is not clear why these events would be so heavily concentrated in the second month of treatment compared to the first; this possibility is considered in more detail in Finding #6. The most plausible explanation is that the difference in discontinuation rates has to do with differences in how patients and their doctors would respond to an apparent lack of efficacy. Because almost all subjects in these clinical studies began with double-blind treatment, those pimavanserin subjects who did not improve in the four- or six-week randomized study could reasonably believe that they received placebo and would, therefore, be inclined to participate in the open-label study to be sure that they did indeed receive the study drug and it did not help. Post-marketing, patients and doctors would know from the beginning that they received active treatment. If they had not improved in six weeks or so, the length of most of the randomized studies, they could conclude with confidence that the drug was not likely to help and discontinue it. Secondly, in the absence of serious adverse reactions, investigators have an incentive to keep subjects in clinical trials, so they can acquire as much data as possible. They also have a less clear idea of when and how to expect any improvement; the cost of treatment is also not an issue for patients in clinical trials. Post-marketing, these incentives do not apply: cost, the toll of minor adverse effects and risk of serious adverse reactions with continued treatment all argue for

discontinuation if the patient has not notably improved. Finally, the post-marketing population is older and is more likely to discontinue due to death or worsening of comorbid conditions. As noted in Finding #1, The expected mortality rate for the post-marketing population is about 2% per month compared to the 0.5% observed during clinical trials.

5. *Beyond the first two months of use, the annualized rate of discontinuation was 50%. Even under the extreme assumption that all these discontinuations were due to deaths, this mortality rate would be consistent with the boxed warning.*

Table 2 shows the rates of discontinuation over twelve-month intervals in the post-marketing population:

Table 2: Discontinuation rates over 12-Month Intervals – Post-Marketing Population

Months	Discontinuation Rate
1-13	69%
2-14	55%
3-15	52%
4-16	50%
5-17	49%
6-18	48%
7-19	48%
8-20	48%
9-21	48%
10-22	45%
11-23	49%
12-24	49%
13-25	50%
14-26	52%

Beginning with the end of the second month of treatment, the annual rate of discontinuation is consistently close to 50%. Even under the extreme assumption that all these discontinuations were due to deaths (rather than drug ineffectiveness, lesser adverse events, financial considerations, etc.) this mortality rate would be consistent with the boxed warning. As noted in Finding #1, an annual mortality rate with antipsychotic treatment of between 32% and 65% would be expected in this population of cognitively impaired elderly patients. If mortality rates among pimavanserin patients were higher than contemplated in the boxed warning, they must be concentrated in the first two months of treatment. This possibility is considered in Finding #6.

6. *The reporting rate of deaths in case reports relative to the total number of patients taking pimavanserin changes little with length of exposure. If pimavanserin were causing a significant number of deaths, those deaths would be more likely to occur*

and to be reported within the first few weeks or months of use.

Of the 885 post-marketing deaths reported, 726 provided information on the length of treatment. Figure 3 shows the reporting rates of deaths by length of exposure as a percentage of patients at risk.

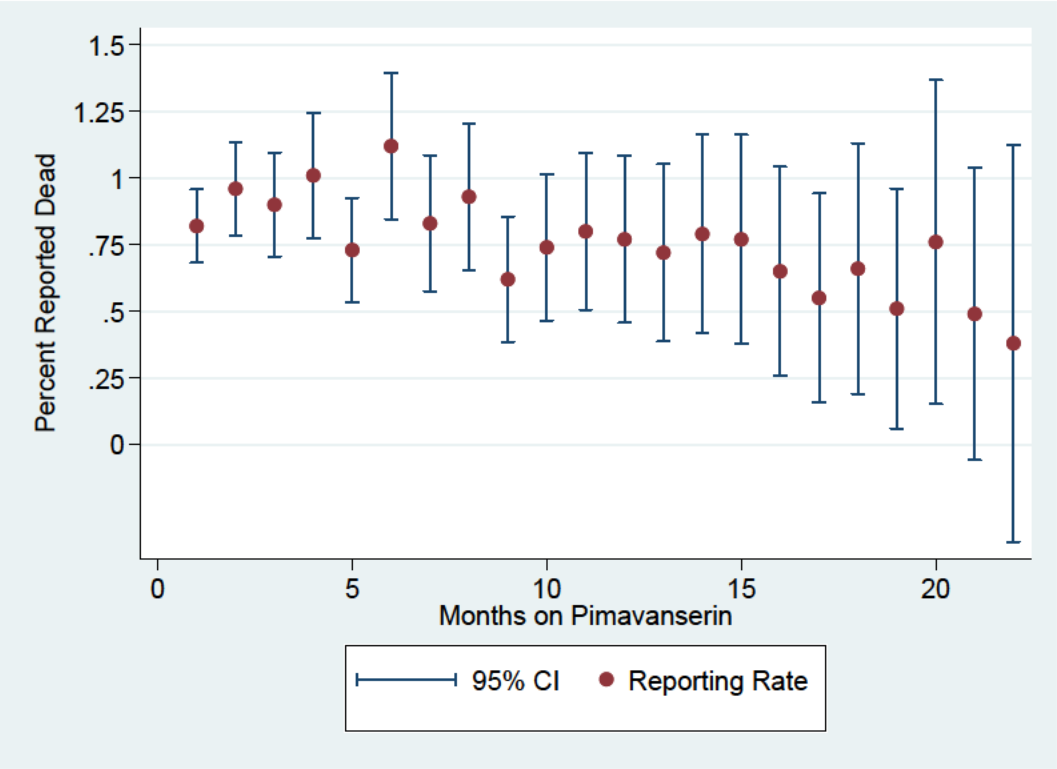


Figure3: Reporting Rates of Deaths in Pimavanserin Patients as a Percentage of Patients At-Risk by Months of Exposure.

Findings #4 and #5 indicate that any unexpected increase in mortality in pimavanserin patients is unlikely to have occurred after the first two months of treatment. Reporting rates for death are also more likely to be higher in the first few months of treatment because adverse events are more likely to be attributed to drug treatment when treatment has been initiated recently. Figure 3, however, shows little concentration of reported deaths within the first few months once the number of exposed patients at-risk is considered. The pattern of death reporting rates in the first months does not correlate with the pattern of discontinuation rates in Figure 1, so the higher rate of discontinuation in the second month of treatment in post-marketing experience compared to the rates observed during drug development does not appear to be due to an unexpectedly high rate of deaths in pimavanserin patients. The very modest fall-off in death reporting rates with length of exposure rather than a steeper decline also suggests that most death reporting was due to routine reporting procedures of the specialty pharmacies rather than a specific concern about the role of pimavanserin in a death.

7. *Review of all the Sponsor's clinical studies did not show any effect on postural changes in heart rate or blood pressure in elderly subjects within the therapeutic*

range. Effects at supratherapeutic dosages were slight for heart rate and not observed for blood pressure.

DPV consulted the Division of Applied Regulatory Science (DARS) as part of a pilot project for identifying potential signals or risks based on data from new molecular entity NDAs. This analysis, based upon structural similarities between pimavanserin and cyproheptadine hypothesized that pimavanserin might cause significant autonomic dysfunction, particularly an increase in orthostatic changes in blood pressure.

To test this hypothesis, we requested a dataset from the Sponsor of all vital sign and drug exposure information on human subjects in the pimavanserin development program. This dataset consisted of 34,719 measurements of heart rate and blood pressure in 2221 subjects. The data were analyzed using a hierarchical mixed effects model treating study and subject within study as random effects. The results are shown in Figures A1-A18 in the Appendix.

The data do show some evidence for a modest increment in orthostatic increases in heart rate with pimavanserin but only with dosages above the therapeutic range (>50 mg). There was no evidence of a greater orthostatic drop in either systolic or diastolic blood pressure with treatment.

8. *Our review of cases showed concomitant use of pimavanserin with other antipsychotic drugs to occur not infrequently. We know of no evidence for clinical improvement in symptoms of Parkinson's Disease psychosis when pimavanserin is combined with other antipsychotic drugs and there is reason to believe that the incidence of adverse events, particularly death, would be increased. Much of the concomitant use, however, appears to be low dosages of quetiapine used off-label as a sleep aid. Such dosages likely have little incremental effect on either risk or benefit.*

The OSE review noted that, of 893 reported fatal cases, there were 147 cases that listed concomitant use of antipsychotics. In 124 (84%) the antipsychotic was quetiapine. There are no studies to our knowledge concerning concomitant use of pimavanserin with other antipsychotic drugs and thus, no evidence for greater efficacy. It is, however, reasonable to assume there is a higher risk with the use of two drugs rather than one, particularly if the dosages are not reduced (in most reported cases the dosage of pimavanserin was either the standard 34 mg dose or not stated).

In a published abstract of a case series of 70 patients prescribed pimavanserin[4], 28 were taking another antipsychotic at the time of initiation of treatment. Ten of these patients had their other antipsychotic tapered to discontinuation over 2-4 weeks and 18 continued the other antipsychotic without tapering. There were 37 who were still taking pimavanserin at the time of the review. Of those 37, 14 were taking quetiapine concomitantly (median daily dose 25 mg) and 1 was taking olanzapine. Although this is not a scientifically representative sample of the population of pimavanserin patients, it appears to be a typical one. In this sample, concomitant antipsychotic use appears to be predominantly quetiapine at a low dosage, well below the dosage (400-800 mg daily)

used to treat psychosis. Quetiapine at this dosage is used off-label as a sedative-hypnotic and likely added little to either the effectiveness or toxicity of pimavanserin.

The OSE review also expressed some concerns about the QT prolongation effects of pimavanserin. A thorough QT study showed pimavanserin to have QT effects in the range not generally considered to be clinically significant by itself but could potentially increase risk if combined with drugs that have more substantial QT effects. Among the reported deaths there are cases of sudden cardiac death, but sudden cardiac death is common in this elderly population with a high prevalence of coronary artery disease. There were no death cases with recognized torsade de pointes or other arrhythmias associated with QT prolongation. The OSE review noted that quetiapine also has a warning for QT prolongation. There are no thorough QT studies for quetiapine but analysis of ECG data from clinical trials has not shown QT prolongation effects on the order of 1-2 milliseconds, well below clinical significance. There are post-marketing reports of QT prolongation in cases of quetiapine overdoses; there are no post-marketing reports of clinically significant QT prolongation in quetiapine patients taking dosages in the therapeutic range. The combination of pimavanserin and quetiapine, particularly with quetiapine dosages in the 25 mg range, is unlikely to cause clinically significant QT prolongation.

IV. CONCLUSIONS

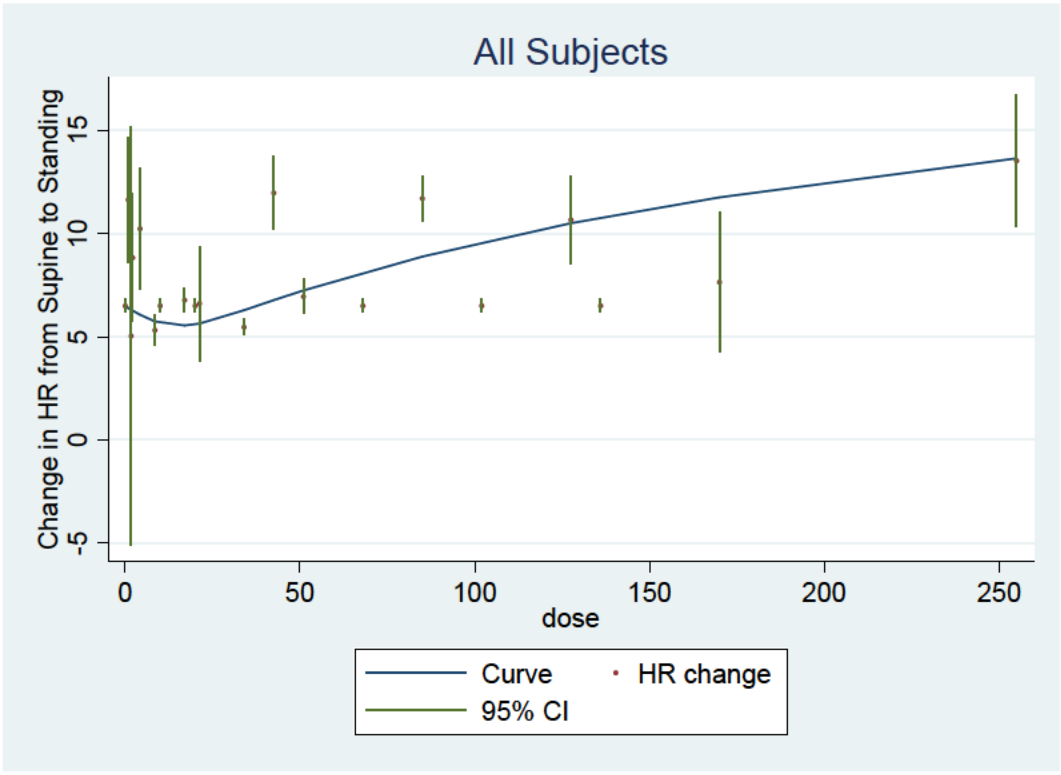
After a review of post-marketing adverse event reports, prescription data, clinical trial data and the medical literature we have no new or unexpected safety findings for pimavanserin. Post-marketing experience has been consistent with clinical trial experience as reflected in current labeling. The large number of reports of deaths and other serious adverse events relative to the size of the patient population can be explained by 1) the high rates of morbidity and mortality in a population of patients with end-stage Parkinson's Disease and 2) high reporting rates for serious adverse events, particularly deaths, which appears to be the result of the practices of the specialized distribution system. At this point there is no basis for further action.

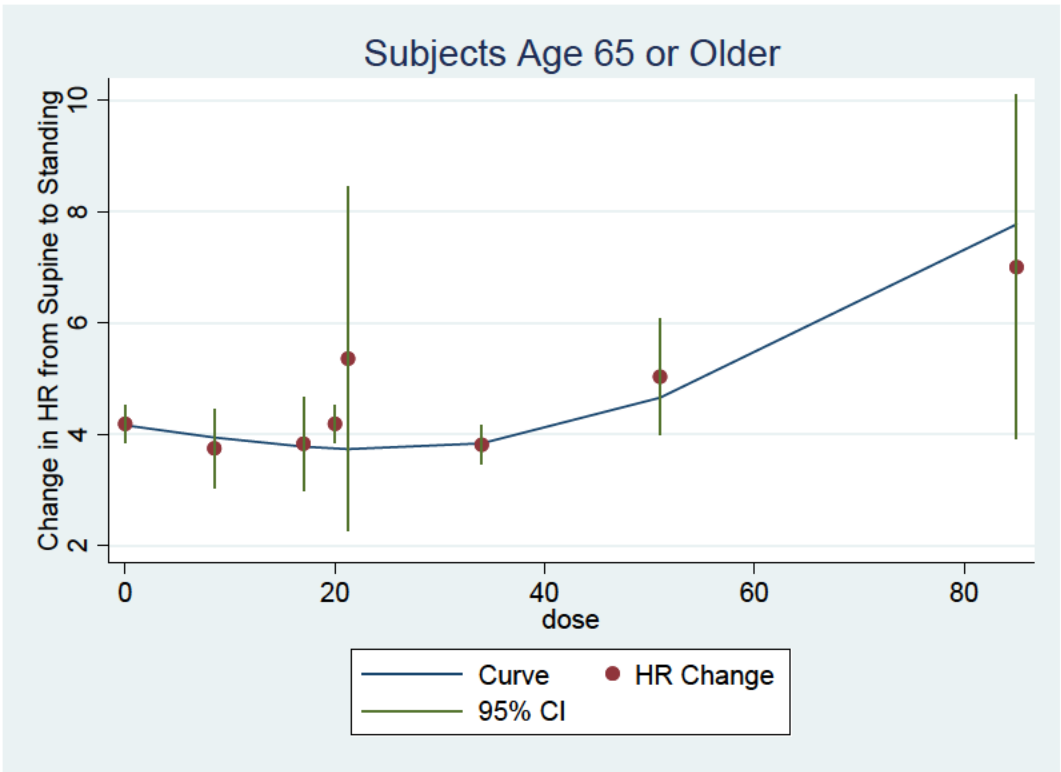
1. Willis, A.W., et al., *Predictors of Survival in Patients With Parkinson Disease.* Archives of Neurology, 2012. **69**(5): p. 601-607.
2. Forsaa, E.B., et al., *A 12-Year Population-Based Study of Psychosis in Parkinson Disease.* Archives of Neurology, 2010. **67**(8): p. 996-1001.
3. Weintraub D, W.A., Torres P, Shim A , Norton J , Liu K, Demos G *Parkinson's Disease Psychosis Associated Comorbidities, and Mortality in the Medicare Population*.
4. Sellers, J., R. Darby, and D. Claassen, *Clinical Experience with Pimavanserin for Treatment of Parkinson's Disease Psychosis (P1.040).* Neurology, 2018. **90**(15 Supplement).

Appendix

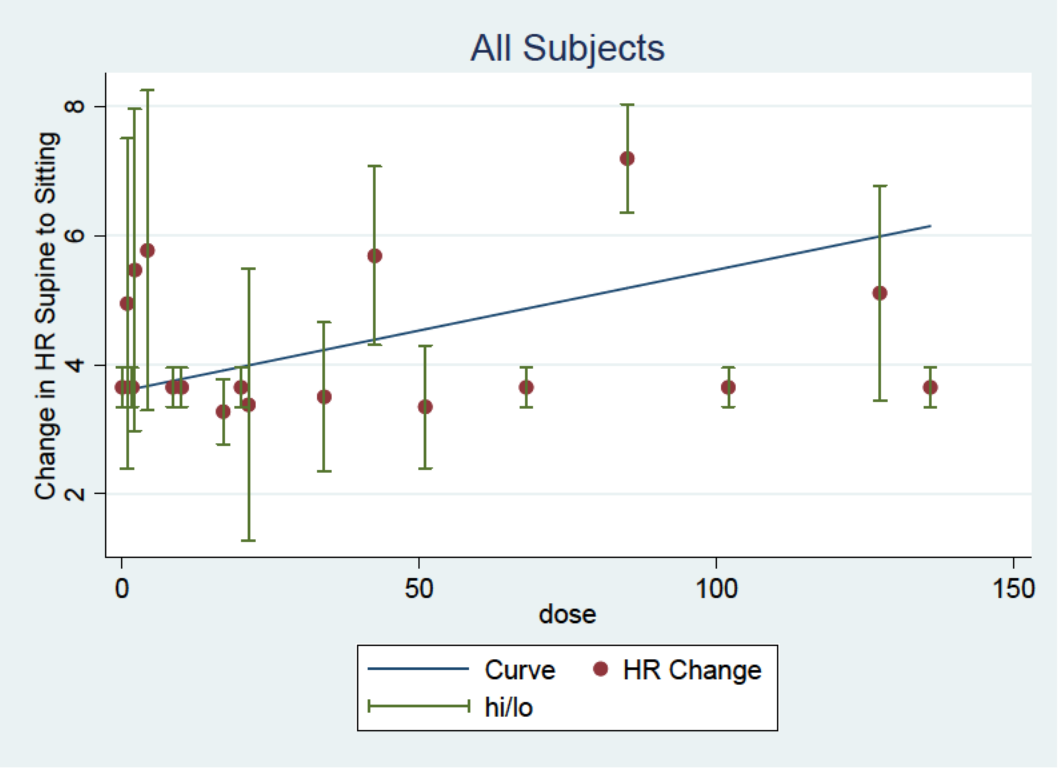
Orthostatic Changes in Heart Rate and Blood Pressure in Human studies of Pimavanserin

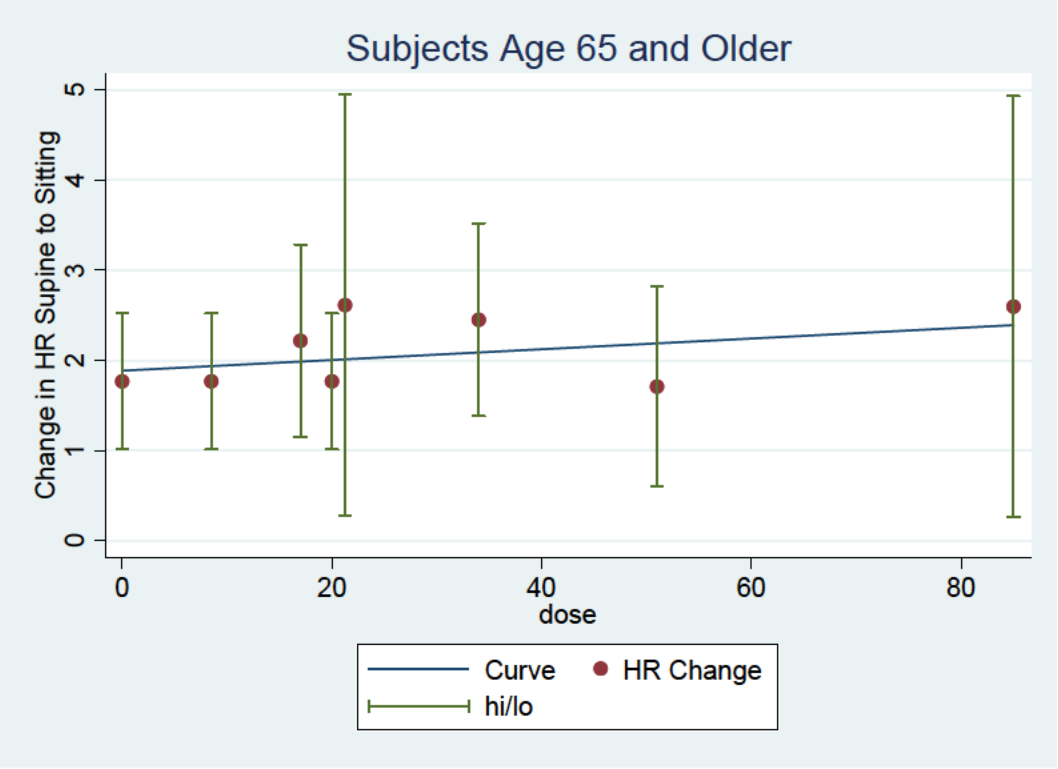
Figures A1 and A2: Changes in Heart Rate from Supine to Standing by Preceding Pimavanserin Dosage



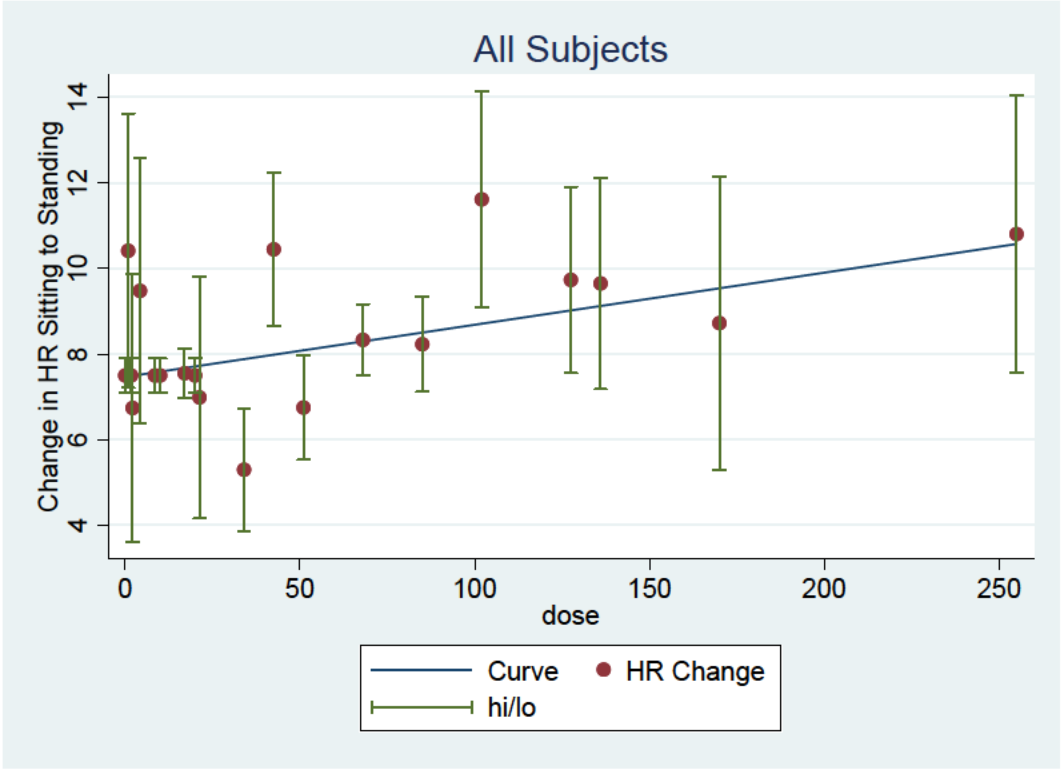


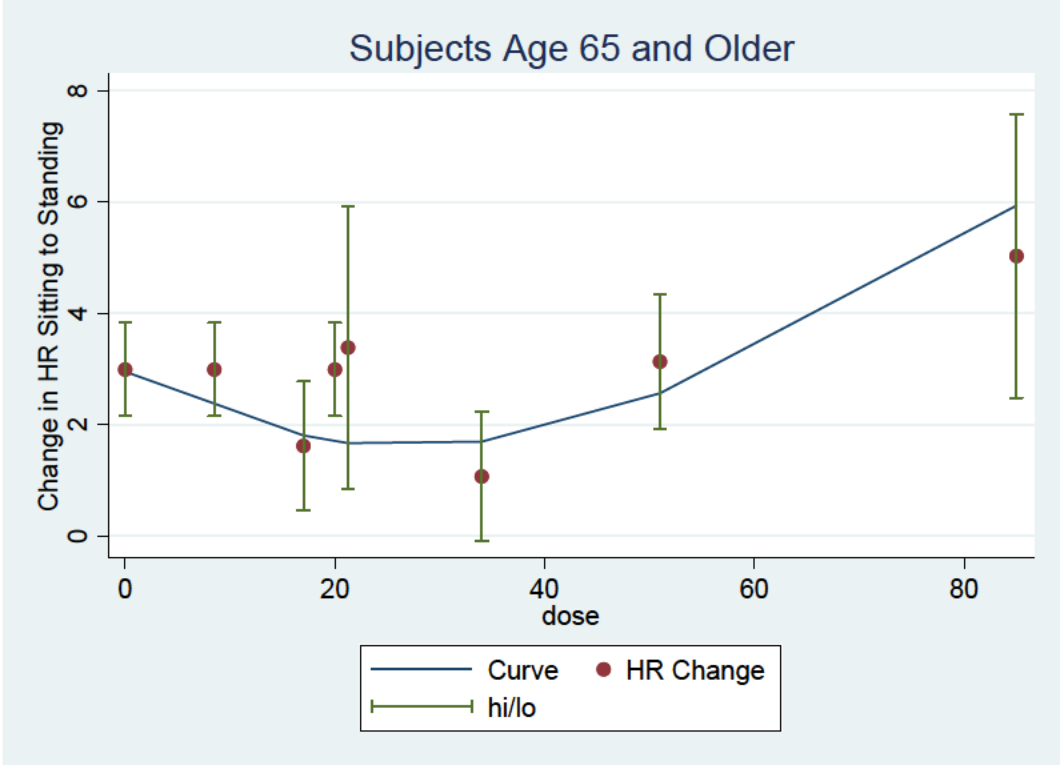
Figures A3 and A4: Changes in Heart Rate from Supine to Sitting by Preceding Pimavanserin Dosage



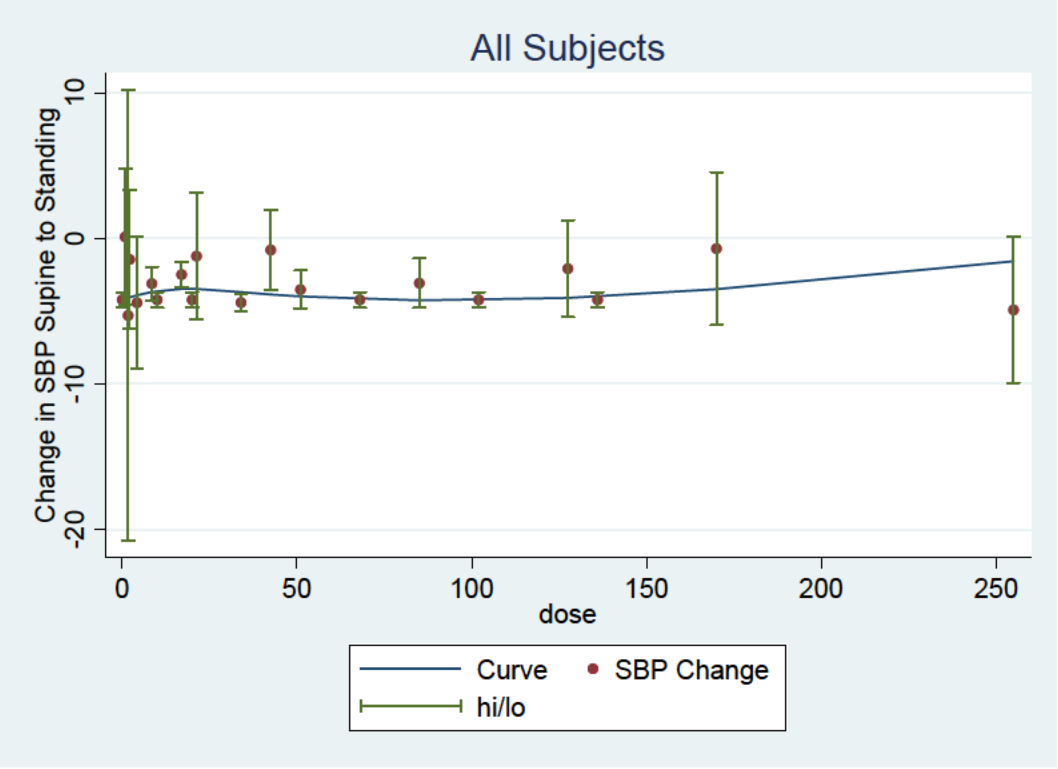


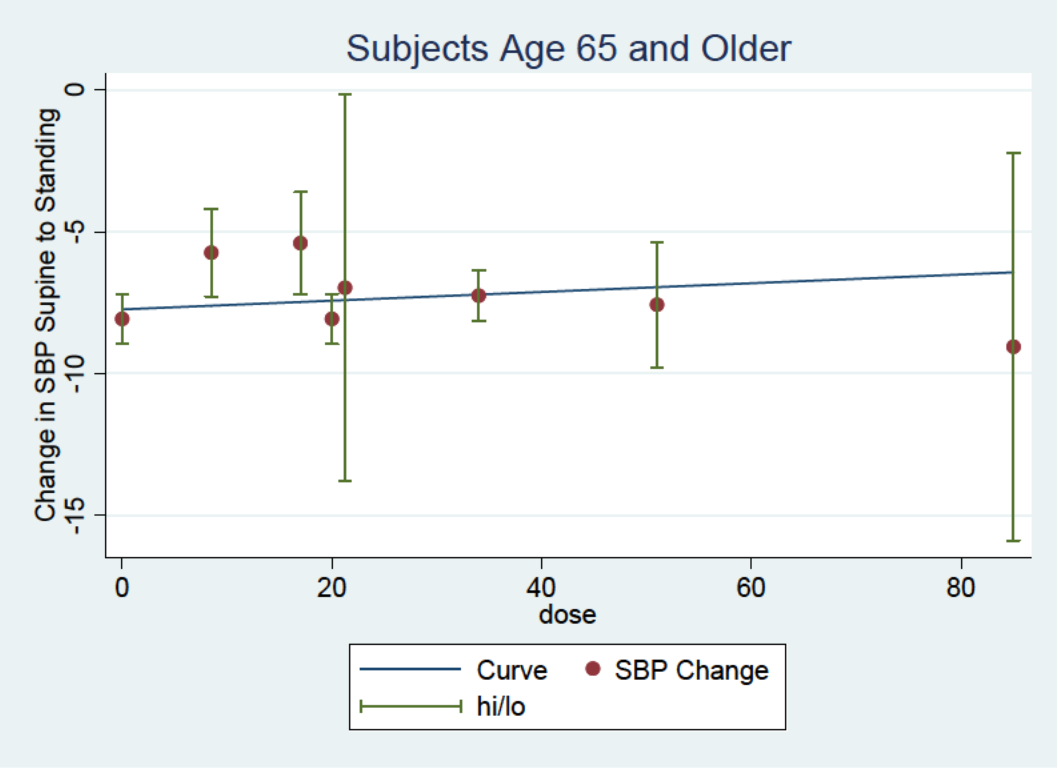
Figures A5 and A6: Changes in Heart Rate from Sitting to Standing by Preceding Pimavanserin Dosage



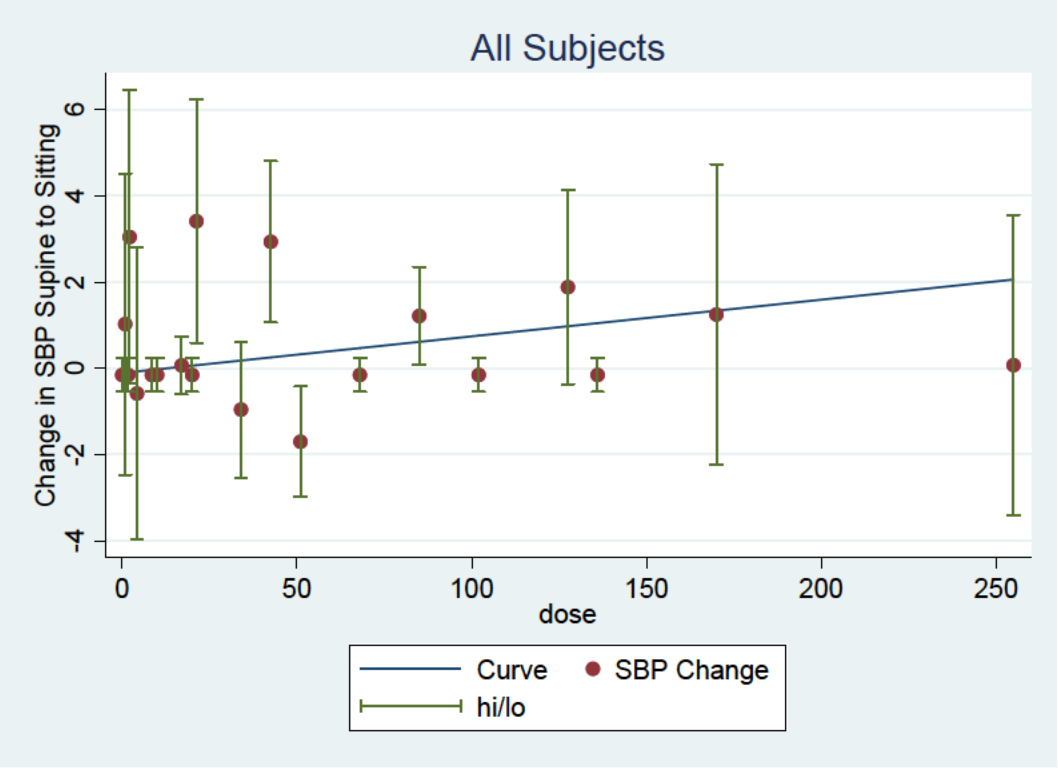


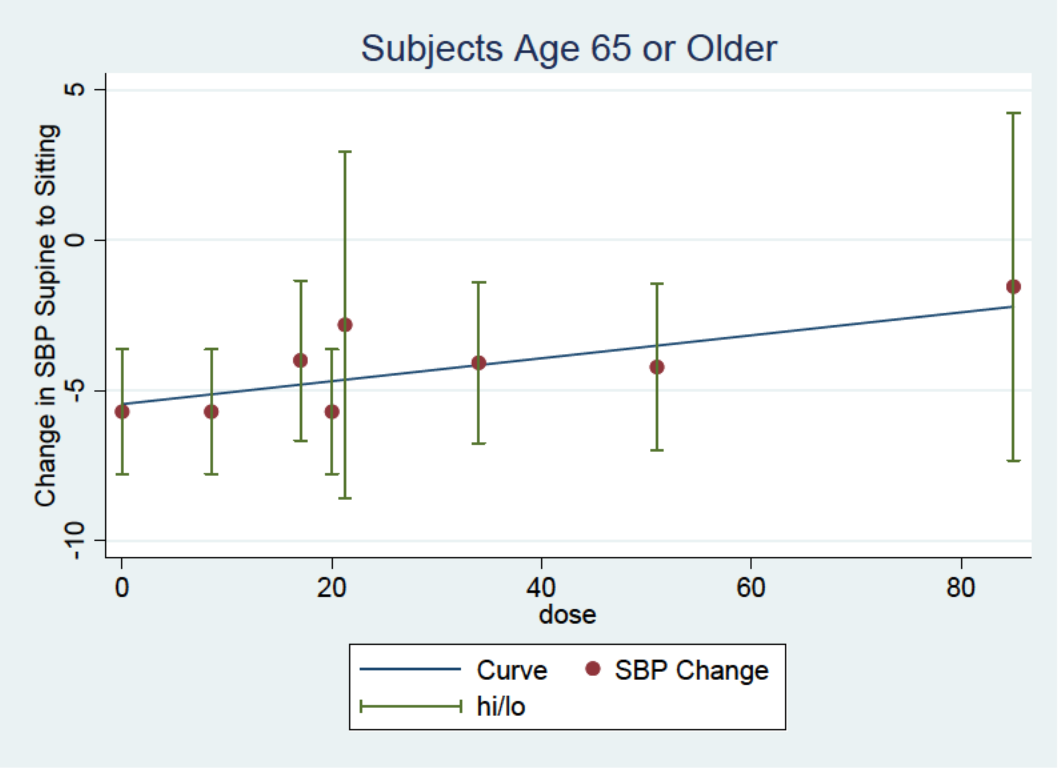
Figures A7 and A8: Changes in Systolic Blood Pressure from Supine to Standing by Preceding Pimavanserin Dosage



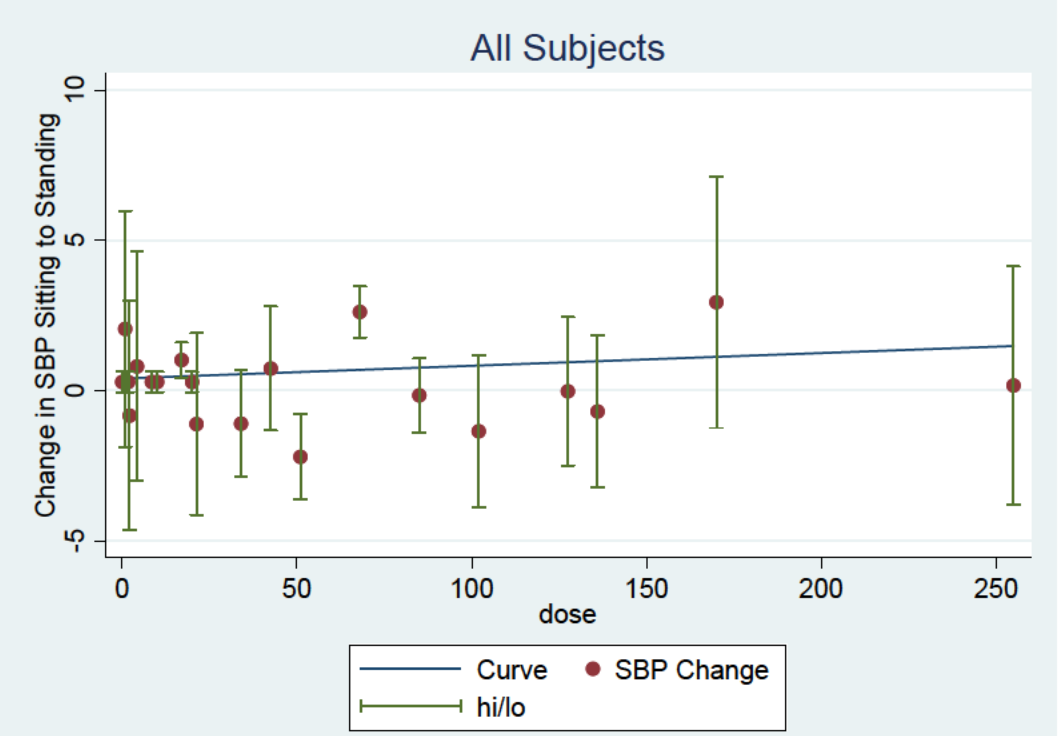


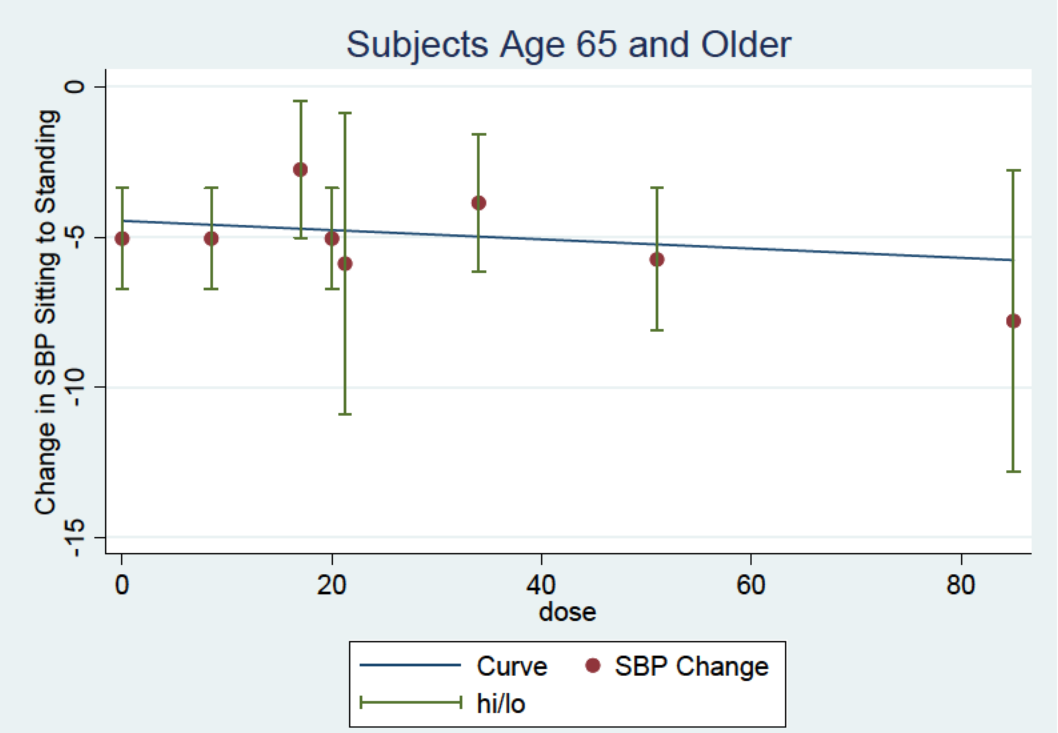
Figures A9 and A10: Changes in Systolic Blood Pressure from Supine to Sitting by Preceding Pimavanserin Dosage



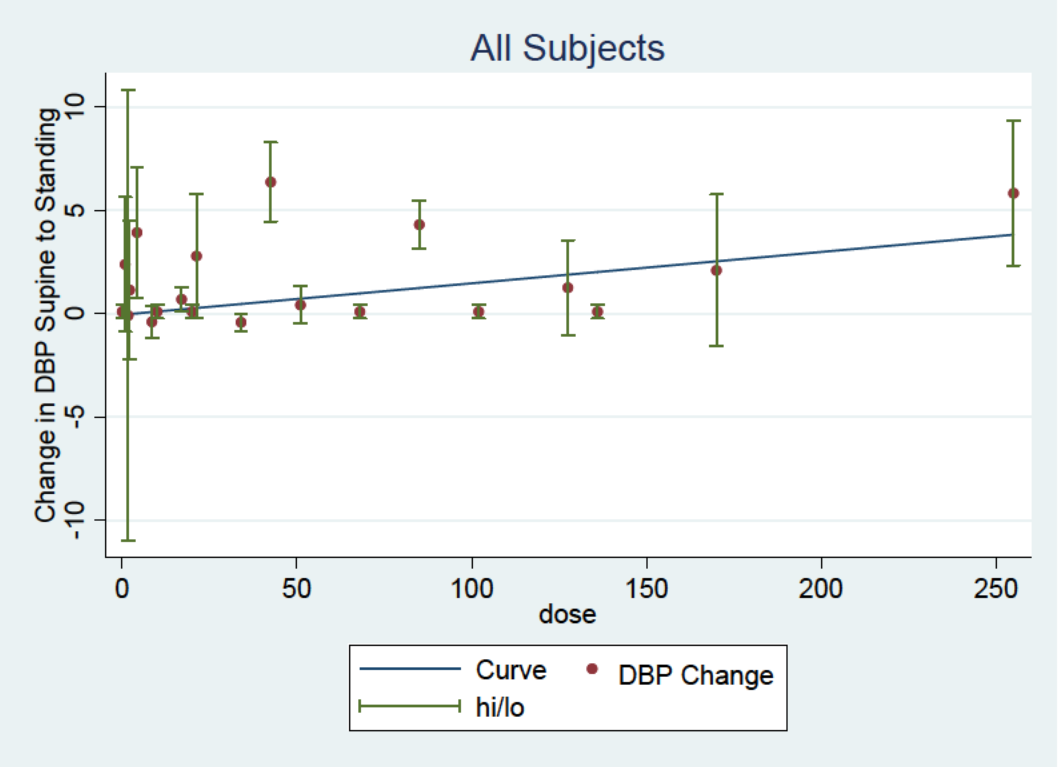


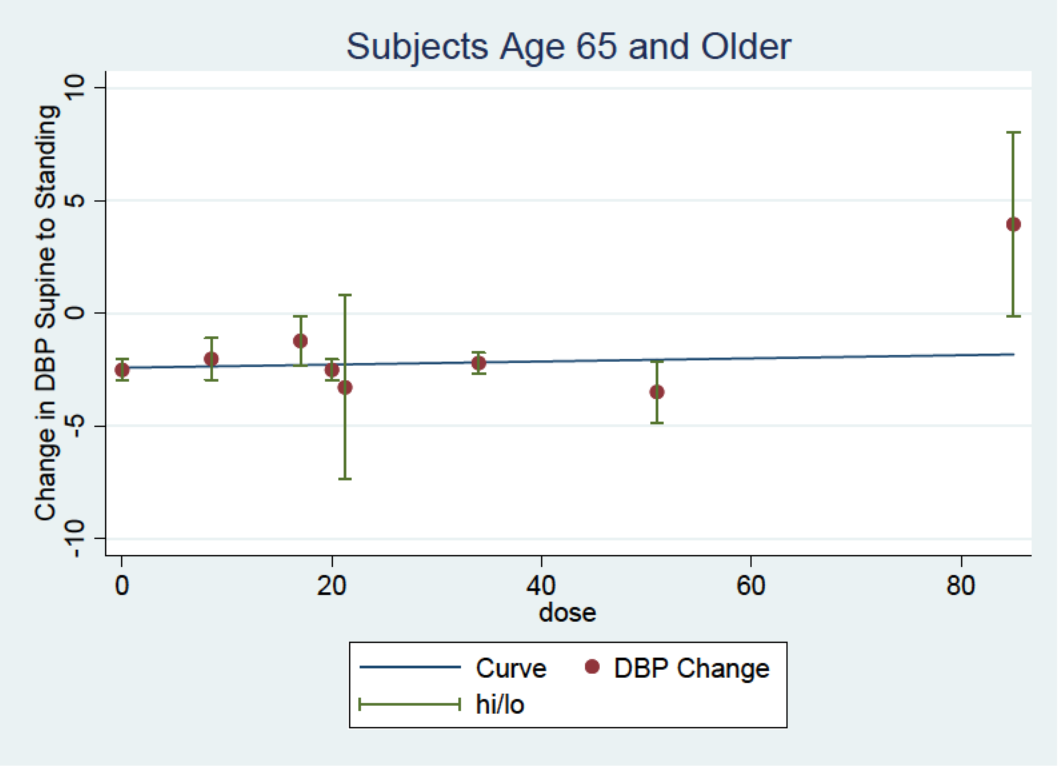
Figures A11 and A12: Changes in Systolic Blood Pressure from Sitting to Standing by Preceding Pimavanserin Dosage



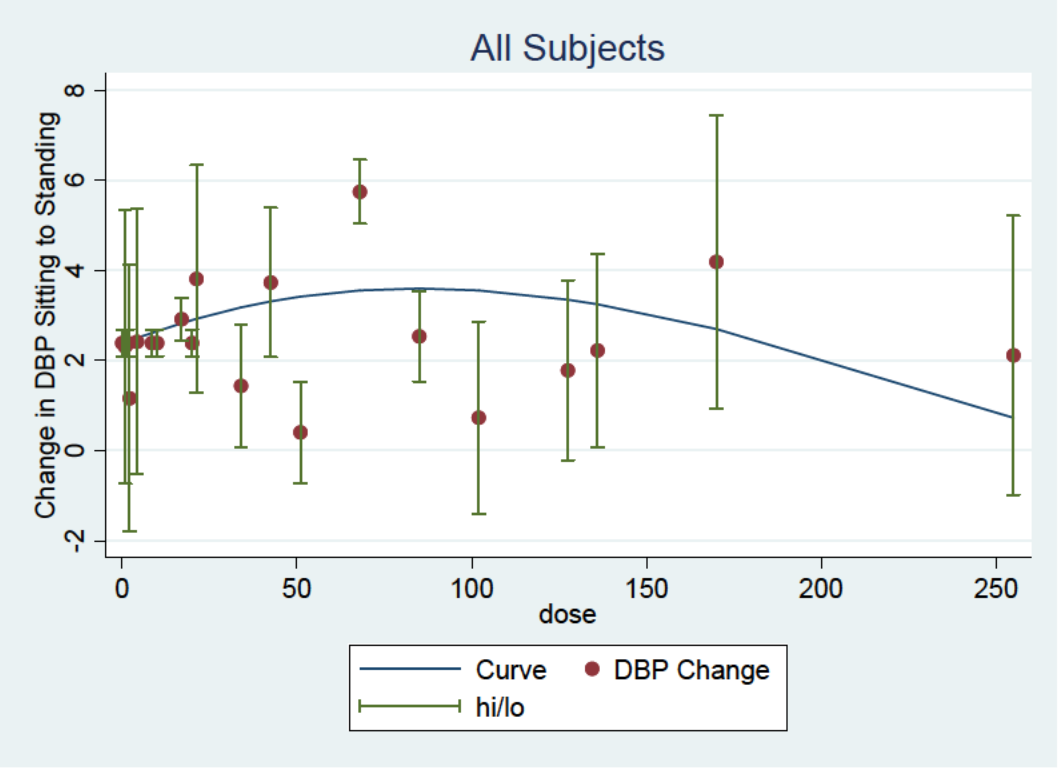


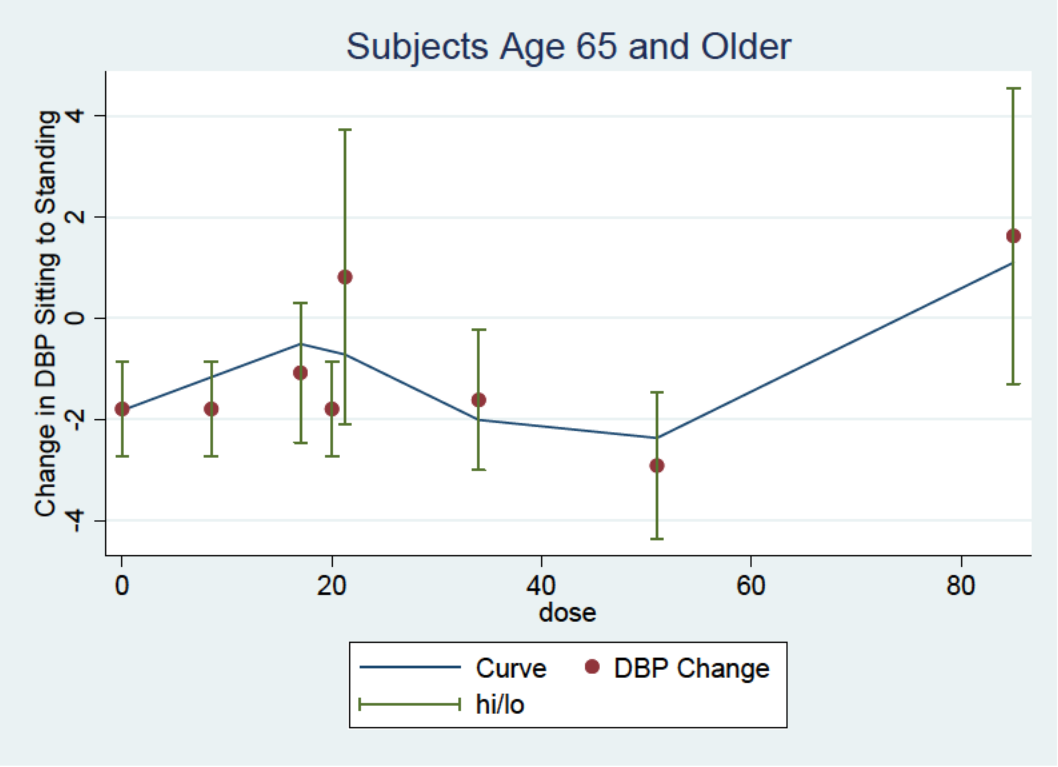
Figures A13 and A14: Changes in Diastolic Blood Pressure from Supine to Standing by Preceding Pimavanserin Dosage



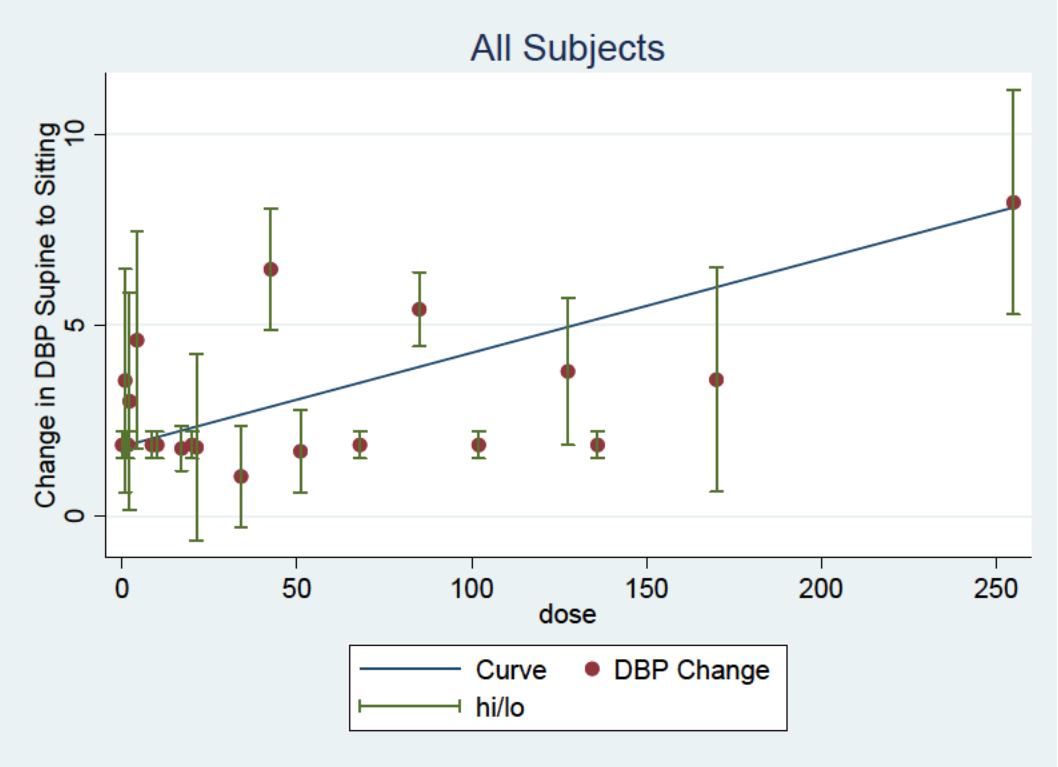


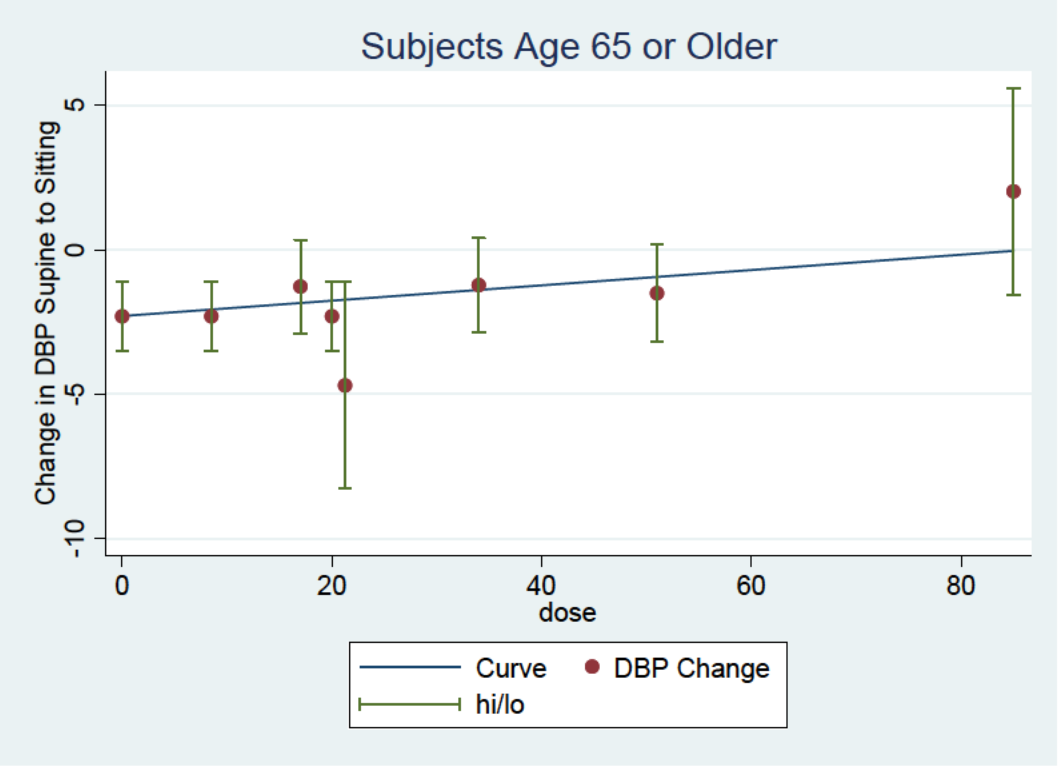
Figures A15 and A16: Changes in Diastolic Blood Pressure from Sitting to Standing by Preceding Pimavanserin Dosage





Figures A17 and A18: Changes in Diastolic Blood Pressure from Supine to Sitting by Preceding Pimavanserin Dosage





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/s/

MARC B STONE
09/17/2018