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Study Title: Percutaneous Tibial Nerve Stimulation-Mirabegron (PTNS-M) Study: A Randomized Clinical Trial Comparing Percutaneous Tibial Nerve Stimulation in Combination with Mirabegron to Percutaneous Tibial Nerve Stimulation Plus Placebo in Women With Refractory OAB Symptoms Study Protocol and Statistical Analysis Plan

Title: A Randomized Clinical Trial Comparing Percutaneous Tibial Nerve Stimulation in Combination with Mirabegron to Percutaneous Tibial Nerve Stimulation Plus Placebo in Women With Refractory OAB Symptoms

Abstract

Introduction: Urgency Urinary Incontinence (UUI) is a common condition with a prevalence of 9-31% in women in the United States. Despite current treatments, a high number of women have symptoms refractory to first- and second-line treatment approaches.

Aims: The primary aim of this randomized controlled trial is to compare the efficacy of percutaneous tibial nerve stimulation (PTNS) and mirabegron treatment versus PTNS with placebo on change in the number of UUI episodes over a 12-week treatment course. Secondary aims include comparing the efficacy of combined treatment of PTNS and mirabegron versus PTNS with placebo on improvement in urinary incontinence symptom specific distress and quality of life related to UUI over a 12-week course of PTNS.

Methods: A total of 54 consented participants will be recruited and randomized with 27 patients in the PTNS with mirabegron (daily 50 mg dose for the 12-week course) group and 27 patients in the PTNS with placebo group. Demographics and baseline data will be analyzed by student's t-test and chi-squared test or Fischer's Exact test as appropriate.

Results: TBD

Anticipated Conclusion: We anticipate that combination therapy will prove superior to monotherapy for reducing the number of UUI episodes over a 12-week treatment course.

Specific Aims:

Introduction/Background: Urgency Urinary Incontinence (UUI) remains a challenging clinical problem for urogynecologists as they treat women and seek to find better therapies. There is a wealth of literature addressing individual therapies for first, second, and third line treatments for UUI. There are three main third line treatment options for UUI including percutaneous tibial nerve stimulation (PTNS), sacral neuromodulation, and intradetrusor botox. At the current time, there are limited studies that have looked at a combination of second and third-line therapy therapies for UUI. While some anticholinergic medications have been studied in combination with percutaneous tibial nerve stimulation (PTNS) such as solifenacin, tolterodine, and trospium, there is limited data on the combination of mirabegron, a beta-3 agonist, and PTNS for treatment of refractory UUI. The studies that looked at anticholinergic medications in combination with PTNS revealed improvement in UUI compared to PTNS plus placebo. However, there are patients who do not tolerate anticholinergic medications well because of side effects. A relatively new finding as reported by the American Urogynecologic Society (AUGS) about avoiding anticholinergic medications in women greater than age 70 secondary to increased risk for cognitive impairment, dementia, and Alzheimer's disease is further impetus to conduct this trial [1]. The rationale for studying mirabegron in combination with PTNS versus PTNS plus placebo is important as mirabegron does not have the significant side effect profile that anticholinergic medications have and better tolerated in the older population. Therefore, more research should be performed to evaluate the effect of the combination of mirabegron and PTNS for refractory UUI. The purpose of this study is to evaluate the combination of PTNS and mirabegron and compare that to PTNS plus placebo in the treatment of refractory UUI.

Hypothesis: Combination therapy of PTNS and mirabegron, a beta-3 agonist, will contribute to greater improvement in the number of urgency urinary incontinence episodes as measured by a 3-day bladder diary compared to PTNS plus placebo in women.

Method: This is a randomized clinical trial comparing the efficacy of combination therapy with PTNS plus mirabegron to PTNS plus placebo in women with refractory urgency urinary incontinence.

Primary Aim: The primary aim of this study is to compare the efficacy of combined treatment of PTNS and mirabegron versus PTNS plus placebo on change in the number of UUI episodes at 12 weeks.

Secondary Aims:

- Comparing urinary symptom specific distress and quality of life over a 12-week course of PTNS.
- Comparing the side effect/adverse event profile of combined treatment of PTNS and mirabegron versus PTNS plus placebo over a 12-week course of PTNS
- Comparing the treatment efficacy and adverse events of combined treatment of PTNS and mirabegron versus PTNS plus placebo in women $\geq$ 70 years of age as a sub analysis within the study

Research Strategy:

Significance: Urgency Urinary Incontinence (UUI), is the complaint of involuntary loss of urine associated with urgency [2], a common condition that affects between 9-31% [3,4] of women and is a significant healthcare burden costing up to 19 billion dollars per year including the costs of over the counter products such as pads and diapers along with medical evaluation and treatment [5]. This condition causes negative impact on sexual and social functioning and can be associated with depression. UUI may be associated with neuromuscular problems and may be associated with anatomical problems, such as large uterine fibroids, pelvic masses, severe uterovaginal prolapse, bladder outlet obstruction, or even severe obesity [6]. First line therapy includes behavioral therapy while second line therapy includes medication with either anticholinergic or beta-3 agonist medications. Anticholinergic medications have long been the mainstay of second-line treatment for overactive bladder (OAB)/UUI, but have significant side effects including dry mouth and constipation [7] which has led to poor patient compliance and high discontinuation rates in clinical practice [8,9]. Likewise, as previously mentioned, the 2021 update from AUGS for OAB recommends avoiding the use of anticholinergic medication in women greater than 70 years old due to negative cognitive effects [1,10,11]. The beta-3 agonist, mirabegron, is better tolerated by the geriatric population, and thus, provides another option that is just as efficacious as anticholinergic medications for combination therapy with PTNS, especially in cases of refractory UUI [11,12].

Refractory UUI indicates consideration of third line therapies. Current third line therapy options include Sacral Neuromodulation (SNM), Onabotulinumtoxin A (Botox) injected into the detrusor muscle during cystoscopy, and percutaneous tibial nerve stimulation (PTNS). Recent interest has peaked with respect to combination of either second and third line therapies or combinations of third line therapies for refractory UUI [13]. Sacral Neuromodulation requires a patient to go to the operating room in order to receive treatment for UUI while Onabotulinumtoxin A (Botox) requires procedural treatment with injection into the detrusor muscle and carries increased risk of urinary retention and urinary tract infection. A recent retrospective observational cohort study of adult female patients with OAB looked at the delay between stopping second line therapy and starting the initiation of third line therapy [14]. Their conclusion was that women with OAB who undergo third-line therapy do so on average more than 3 years after starting medications. Time to third-line treatment is largely driven by the number of antimuscarinic medications tried and timing of diagnostic evaluation by a specialist. They found that predictors of shorter time to third-line therapy included younger age, delayed gastric emptying, diabetes, bothersome side effects of antimuscarinics, earlier specialist evaluation and diagnostic testing, and mirabegron use [14].

Some patients would prefer a less invasive treatment such as PTNS to more procedural modalities of SNM and Botox. Scientific professional society guidelines advise PTNS as a third line treatment [15]. PTNS has been validated via sham-based trials, as a third line option with

proven benefit that is less invasive than the other third line options for management of UUI. Although researchers have studied PTNS, Botox, and SNM alone and have seen benefit for patients, recent interest has peaked into the efficacy of combination therapy. Further studies are needed regarding combination therapies, particularly those including third line modalities [13].

PTNS in combination with anticholinergic medications has been studied and outcomes compared [16,17,18,19]. In most of these studies, when PTNS plus placebo is compared to PTNS in combination with an anticholinergic medication, the combination therapy was found to be more effective than PTNS plus placebo or an anticholinergic medication alone (Table 1). In previous systematic reviews, when PTNS alone was compared to medications (anticholinergics) alone, no difference was found and each monotherapy was considered to be equally efficacious [20,21].

Table 1: Summary of studies looking at combination of PTNS with anticholinergic medications

Author	Comparison	N	Results
Vecchioli-Scaldazza et al., 2018 [16]	Solifenacin versus posterior tibial nerve stimulation (PTNS) versus combination therapy (PTNS+solifenacin)	27	OAB-SS (overactive bladder symptom score) solifenacin vs. PTNS p=0.0039 solifenacin vs. solifenacin+PTNS p=<0.0001 PTNS vs. solifenacin+PTNS p=0.009 PGI-I (patient global impression of improvement SS vs. PTNS p=0.0017 SS vs. SS+PTNS p=<0.0001 PTNS vs. SS+PTNS p=0.0002
Sancaktar et al., 2010 [17]	Tolterodine alone vs. stroller afferent neuro-stimulation (SANS)+Tolterodine	38	UUI episodes (per week) before therapy after therapy p Tolterodine alone 22.8±2.4 12.3±0.8 <0.001 Tolterodine+SANS 22.4±2.8 6.4±0.5 <0.001 P >0.05 <0.001
Eftekhar et al., 2014 [18]	Tolterodine alone vs. PTNS+Tolterodine	30	Comparison of UUI symptom specific distress pre vs. post treatment PTNS+tolterodine vs. tolterodine (p=0.03)
Kizilyel et al., 2015 [19]	PTNS vs. Tolterodine vs.PTNS + Tolterodine	30	Reduction in # of UUI episodes most significant in PTNS+tolterodine PTNS plus placebo (p<0.01) Tolterodine (P<0.05) PTNS+Tolterodine (P<0.001)

Because the older population of women is a major focus of this study, it remains important to focus on less invasive treatments that are better tolerated by the geriatric

population as a whole. Therefore, because PTNS offers a less invasive approach to third line therapy and because mirabegron does not have the negative cognitive effects that anticholinergic meds cause in the geriatric population, this combination of PTNS + mirabegron offers great potential for providing better treatment for UUI/OAB, especially in women 70 years of age or greater.

Given the significant burden associated with UUI/OAB expecially in older women, combination therapy of less invasive approach and with PTNS and the mirabegron has fewer adverse effects and may provide improved efficacy, adherence, and safety.

Innovation: The main innovation for this study will be the combination of PTNS with mirabegron. Further research needs to occur on combination therapy that can be offered on an outpatient basis to patients that either do not desire to have an invasive procedure or are not optimal surgical candidates. Based upon the previous studies looking at combination therapy with PTNS and anticholinergic medications, one can see that PTNS in combination with medication is more efficacious than either medication alone or PTNS plus placebo (Table 1). While mirabegron is contraindicated in patients with uncontrolled hypertension, overall, patients tolerate it better than anticholinergic medications. Thus, mirabegron offers hope as a better medication combination with PTNS for all age groups of patients. This study also involves looking at the efficacy of combination therapy of PTNS and mirabegron in the geriatric population $\geq$ 70 years of age, as mirabegron has not been associated with the exacerbating symptoms of dementia that anticholinergic medications do within the geriatric population [1,11,12]. Therefore, studying mirabegron in combination with PTNS offers great hope for the treatment of refractory UUI in the geriatric population.

Approach:

Study Design

A randomized controlled clinical trial with female patients consented at the University Alabama at Birmingham (UAB) facilities. The study will evaluate female patients with UUI that are refractory to second-line treatment or who cannot tolerate anticholinergic medications. Patients will complete a 3-day voiding diary prior to the 12-week treatment of PTNS (at baseline) and at the completion of the 12-week treatment with PTNS.

Inclusion Criteria

- Female patients $\geq$ 18 years old at UAB facilities with refractory urgency urinary incontinence that have failed first line and second line treatments
- Ability to consent
- Ability to complete all study related items and interviews

Exclusion Criteria

- Patients with a history of any known or determined urinary retention or urinary tract obstruction
- PVR > 150 ml in clinic prior to the start of PTNS
- History of bladder augmentation surgery
- Patients who are pregnant or who have the suspicion of pregnancy

- Uncontrolled hypertension
- Hypersensitivity to mirabegron
- Superficial and/or deep skin infection where PTNS intervention is required
- Spinal cord injury or clinically significant neurological disorders known to affect urgency urinary incontinence
- Bleeding diathesis
- Failure of previous third line treatment options such as sacral neuromodulation, PTNS, or Botox
- Pacemaker, implantable defibrillator
- Current use of Interstim sacral nerve stimulator or TENS in the pelvic region, back, or legs
- Coagulopathy
- Chronic swollen, infected, inflamed skin or skin eruptions (e.g., phlebitis, thrombophlebitis, varicose veins) in the region where the PTNS needles or surface electrodes would be placed
- Metal implant in foot/toes near TENS electrode location
- Marked sensory deficit (numbness) of feet or ankles in the region where the PTNS needles or surface electrodes would be placed
- Currently pregnant or planning to become pregnant during the course of the study
- Unwilling to use acceptable form of contraceptive if the participant is of childbearing potential
- Unable or unwilling to complete the 3-day bladder diary
- Visual impairment prohibiting reading the paper diary
- Inability to provide informed consent, complete questionnaires independently, or to attend intervention sessions
- Unable to speak, read, or write in English

Intervention

Prior to beginning the treatment intervention, patients who are currently on medical therapy will stop medical therapy 2 weeks prior to the start of the trial. One arm of the study will receive PTNS combined with mirabegron and the other arm of the study will receive PTNS with placebo. In the PTNS with mirabegron arm, the patient will take a 50 mg dose daily for 12 weeks of the trial. In the PTNS with placebo arm, the patient will receive a placebo daily during the 12-week trial. PTNS will be performed as described: The percutaneous approach entails insertion of a 36-gauge needle electrode at a 60 degree angle approximately 5 cm or 3 finger breadths cephalad to the medial malleolus and posterior to the tibia. A portable electrical stimulator delivers an adjustable current in the range of 0.5-9 mA. The generators commonly are set for a pulse frequency of 20 Hz with a goal of creating a motor and/or sensory response in the foot. The stimulation sessions last for 30 min once per week for 12 continuous weeks.

Primary Outcome

Change in the number of UUI episodes over a 3-day voiding diary pre- vs. post-treatment.

Secondary Outcomes

- Number of voids on a 3-day voiding diary pre- vs. post-treatment

- Number of stress urinary incontinence (SUI) episodes pre- vs. post-treatment on a 3-day voiding diary
- Change in symptom distress as measured by the Urinary Distress Index (UDI-6) questionnaire pre- vs. post-treatment
- Change in UUI/OAB quality of life as measured by the Incontinence Impact Questionnaire Short Form (IIQ-7) and Overactive Bladder Questionnaire-Short Form (OAB-q SF) questionnaires pre- vs. post-treatment
- Adverse Events

Protocol in detail

Women seen in the Urogynecology and Urology clinics at the University of Alabama at Birmingham who are seeking treatment for refractory UUI symptoms will be screened. Patients who have failed a credible behavioral therapy intervention and medical therapy or not tolerating medical therapy will be evaluated for this study. Those patients satisfying the inclusion/exclusion criteria will be offered participation. Informed consent will be reviewed and signed with patients wishing to proceed.

At enrollment, any subjects who are using medical therapy including anticholinergic or β3 agonist medications will stop these therapies for 2 weeks prior to treatment. Baseline clinical data including a 3-day bladder diary, OAB-q-SF, IIQ-7, UDI-6, and a pain catastrophizing scale after washout as indicated will be collected as well as clinical and demographic information. Data from subjects' urodynamic testing will be abstracted from the clinical chart if performed within the prior 12 months of the enrollment date. If no urodynamic testing is available then this data will not be collected for those subjects. Subjects will be randomized the day of the first scheduled PTNS appointment. Subjects will be blinded to which group they are assigned.

Subjects will be randomized to the PTNS with mirabegron group or to PTNS plus placebo group. The PTNS with mirabegron group will undergo one PTNS treatment per week for 30 minutes, will start taking 50 mg daily of mirabegron on the day of the first PTNS procedure and will continue the daily 50 mg dose for the duration of the 12 week PTNS trial. The PTNS plus placebo group will take the placebo starting the day of the first PTNS treatment and will take the placebo daily for the remainder of the 12-week clinical trial.

Subjects will fill out a 3-day voiding diary immediately post-treatment after the last session of PTNS. The patient will also complete the OAB-q-SF, IIQ-7, and UDI-6.

Randomization/Allocation

Patients will be randomized to the PTNS with mirabegron group or PTNS with placebo group in a 1:1 fashion using variable size permuted blocks of 2, 4, and 6. A sequentially numbered sealed envelope will be selected to reveal the randomized intervention. This will be done by a member of the research team on the day of the first PTNS treatment. Subjects will be blinded to which group they are assigned. Allocation concealment will be ensured by using a centralized service to provide sequentially numbered, opaque, sealed envelopes.

Sample Size Calculation

The main hypothesis is that the women in the PTNS with mirabegron group will have more improvement in the number of UUI episodes than women in the PTNS plus placebo group. Given this hypothesis, based on existing data,[17] a 2-sided alpha=0.05, the estimate for that difference in improvement has been estimated to be 2.5 UUI episodes over a 3-day bladder diary pre-vs. post-treatment with a standard deviation of 3 and a power of 0.80. Assuming an attrition rate of 10%, the total N per arm is estimated to be 27 subjects (a total of 54 subjects) for this study. The sample size estimation results are summarized in Table 2.

Table 2: Power analysis for change in UUI episodes pre-vs. post-treatment

Detectable △	Standard Deviation	Power	N
2.5	2	0.85	13
2.5	2	0.90	15
*2.5	3	0.80	24
2.5	3	0.85	27

Data analysis

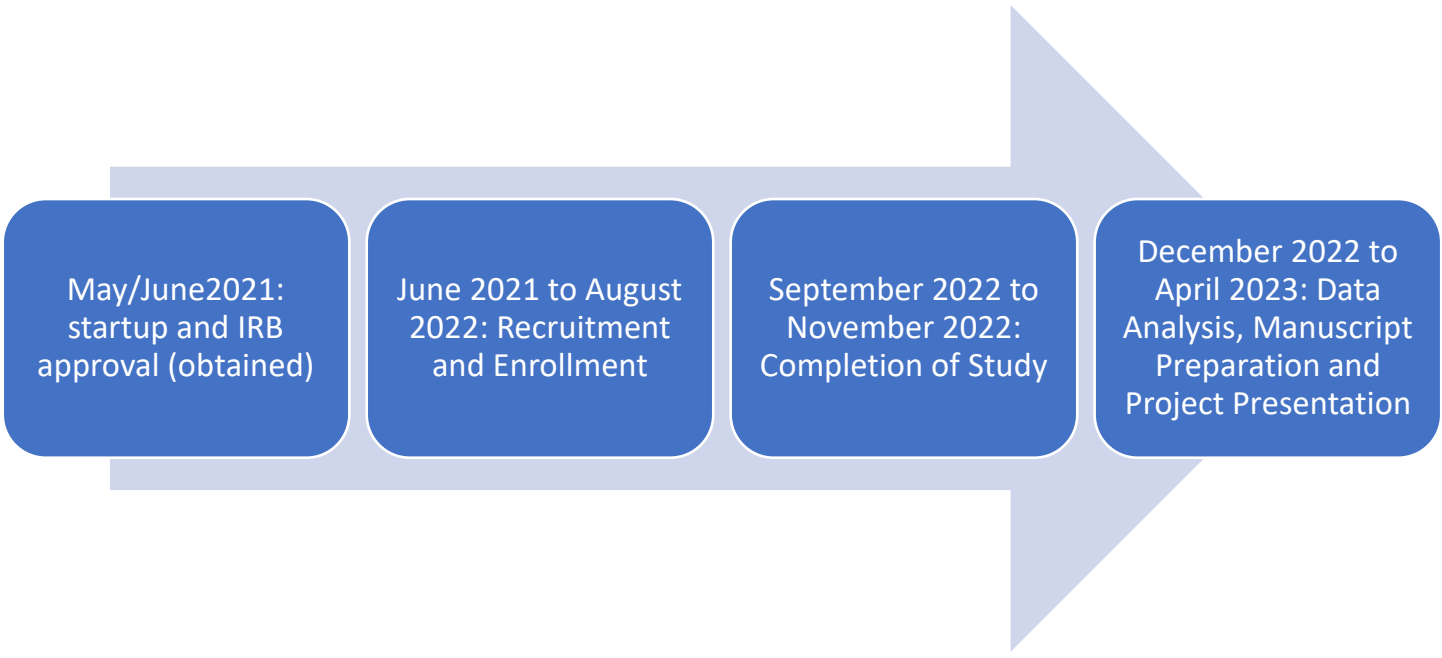
For the primary analysis, an intention-to-treat analysis including all eligible patients randomizing to treatment will be used. Baseline clinical and demographic data will be compared between groups. The primary outcome (changes in the number of UUI episodes pre- vs. post-treatment) will be compared via general linear models.

Potential Pitfalls

The plan is to recruit 54 subjects based on the estimated sample size over a 12-18 month study period. Recruitment will be accomplished through multiple co-investigators in the division of

Urogynecology and Pelvic Reconstructive Surgery. An adequate sample size over the study period based on our experience from previous studies is feasible. The average number of patients per year between Urology and Urogynecology receiving PTNS is between 50 to 70. The Division of Urogynecology has an established clinical research team with clinical nurses and nurse coordinators dedicated to clinical trials and will regularly monitor the recruitment process to achieve our study enrollment goal. Our team has a strong interdisciplinary relationship between Urogynecology and the Continence Clinic of the Department of Geriatrics and we do not anticipate problems with study enrollment. We have an excellent research track record as one of the Pelvic Floor Disorder Network sites, our center has successfully recruited women with urgency urinary incontinence symptoms for the Anticholinergic Therapy vs OnabotulinumtoxinA for Urgency Urinary Incontinence trial (ABC trial) and the OnabotulinumA vs Sacral Neuromodulation on refractory Urgency Urinary Incontinence in Women trial (ROSETTA trail) [22,23]. Compared to antimuscarinics, the insurance coverage for mirabegron is difficult and presents a major obstacle to patients being able to receive mirabegron. To overcome this issue, the study will provide the medications. Given the need for further treatments for refractory UUI, these study outcomes will be a significant contribution to the current literature and have the potential to influence clinical care.

Timeline



I am currently in my first year of fellowship and if I did not remain at the institution following fellowship, I would still be principal investigator and direct this study. We have a strong research team including co-investigators in the Urogynecology Division, FPMRS fellows, research nurse coordinators, and nurses dedicated to research trials. All are focused on maintaining a solid infrastructure for success.

Regular research meetings will take place with the team throughout the trial with review of clinics to identify possible patients and to ensure delegation of tasks for completion of enrollment and follow-up. We will also advertise the study on a currently existing social media research site and in existing UAB internet periodicals and the Birmingham newspaper. I will also be actively involved in the statistical analysis with the assistance of the Center for Clinical and Translational Sciences (CCTS) and Center for Women's Reproductive Health (CWRH) at UAB. My dedication to this project and the research infrastructure in our division will assist in seeing this project through to completion.

Impact for Future Study

Another future innovation in this study draws upon a supplementary study to NOTABLe, a Pelvic Floor Disorders Network study evaluating PTNS vs. sham treatment for fecal incontinence. Genetic polymorphisms associated with placebo effect in the treatment of fecal incontinence were assessed [personal communication, Richter]. This supplementary study to NOTABLe assessed the relationship between response to PTNS or sham treatment and genetic single nucleotide polymorphisms (SNP) associated with treatment response via the COMT val158met genetic polymorphism. In the future as this current study evolves, we would like to have patients from both arms of the study provide blood samples that one can utilize for further analysis characterizing the relationship between SNPs and treatment response. This supplemental analysis will add to the growing literature on the placebome and provide critical information for planning future pelvic floor studies that account for the variation in an individuals' likelihood of being a placebo responder.

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Statistical Analysis

This was a randomized controlled trial Double Blinded (providers and patients) looking at PTNS+Myrbetriq vs. PTNS+Placebo. The original sample size calculation noted that we needed 12-15 in each arm. That was the original one done by Kimberly Martin. We went ahead and randomized 27 in each arm for a total of 54. We had 7 fall out in the Active Arm and 1 fall out in the Placebo Arm. The reason for fall out was noncompliance with coming to the 12 weeks of visits and not any issues related to SAEs.

We had 20 complete in the Active Arm and 26 complete in the Placebo Arm. You all have the data sheet. We have complete data for all initial visits. The 8 patients that we do not have End of Study Data for are the ones who fell out after randomization.

So, for statistical analysis, we have the Demographic Data as I have listed and we want comparisons between the two groups as one would do in an RCT. Secondly, the primary outcome is the change in the

number of UUIs (urge urinary incontinence episodes) over a 3 day bladder diary pre-trial to the number of UUIs post-trial on a 3 day bladder diary. Then compare them between the two groups.

Other components of the 3 day bladder diary include number of SUI (stress urinary incontinence) episodes changes pre vs. post, number of daytime voids pre vs. post, number of nighttime voids pre vs. post, and number of pads used pre vs. post.

Secondary outcomes also include the questionnaires of IIQ7, UDI 6, and OABQSF changes pre vs. post-trial and comparing them.

This should be laid out in the data table.

Thank you!

Dr. Stanley