17-Hydroxyprogesterone Caproate (OHPC) in Hormone Replacement Therapy (HRT): Endometrial Suppression and Fibroid Reduction with Negligible Side Effects

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Running title: OHPC in HRT

Keywords: OHPC, HRT, fibroids, estradiol cypionate

This paper has been submitted and rejected to multiple peer-reviewed journals. Reviewer's comments and my response is included in an appendix. The ultrasound reports and scans are available upon request.

It should be clear from the comments that the paper is unpublishable not because of any technical flaws, but because the protocol described so grossly exceeds "standard of care" HRT that reviewers are incapable of seeing the value of a nonsurgical treatment for a condition (fibroids) for which there are currently no viable nonsurgical alternatives. It should also be clear that the reviewers for these journals are completely incompetent in the field of HRT as it is practiced by elite physicians today, and in many cases, in the field of living as a modern human being where things like cost of treatment and Quality of Life take priority over academic purity.

I therefore am releasing this work to the Public Domain so that people can benefit from it directly without having to wait for these gatekeepers of information to catch up to the state of the art in HRT. Check https://www.frailproof.com or do an Internet search for "Frail Proof" for up to date information on the protocol and other HRT information.

Cover letter (disclosure)

I, Scott Raney (the lead author) ORCID iD 0000-0003-0667-4498, submit our manuscript "Hydroxyprogesterone caproate (OHPC) in hormone replacement therapy (HRT): Endometrial suppression and fibroid reduction with negligible side effects" for your consideration. We believe it will be an important contribution to the field because although OHPC has been widely used in clinical practice for a variety of purposes for decades, there are no previous reports of it being used in a continuous HRT protocol, nor of its remarkable and potentially unique ability to reduce leiomyomas (fibroids). We include background information and references to other uses of OHPC and on the effects other progestins have on fibroids because these may not be well known.

This manuscript is not under consideration by any other journal and will not be submitted elsewhere unless you decline to publish it. No portion of this manuscript has been published previously nor has any information about the underlying study been published or discussed at any conference or other meeting.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

This study is based on data from a private practice and was not industry sponsored or subject to institutional review, no funding was provided by any outside entity, nor do we have any other financial conflict of interest. We have a signed release from the patient/subject/participant available to you upon request.

We have included ultrasound reports documenting the endometrial protection and fibroid reduction for the benefit of the reviewers. These may be included in any published version of this paper at your discretion.

Regards,

Scott Raney, PhD.

Abstract

Background: The aim of the study was to determine if 17-hydroxyprogesterone caproate (OHPC) provides endometrial protection in an injection-based continuous hormone therapy (HRT) protocol.

Methods: OHPC, testosterone cypionate, and estradiol cypionate were provided to a postmenopausal woman by injection to achieve optimal serum levels, defined to be the top of the lab range for free testosterone, median estradiol levels in premenopausal women (90pg/ml and FSH of 5), and calculated progesterone-equivalent levels of 10ng/ml.

Results: Over a period of 6 years OHPC maintained optimal endometrial thickness and the participant's largest uterine fibroid was reduced to non-detectability. Participant reported a high level of satisfaction with the protocol and no adverse events were reported.

Conclusion: OHPC has advantages over bioidentical progesterone and other progestins for HRT, particularly in cases where fibroids are an issue.

Keywords: HRT, MHT, injection, estradiol cypionate, fibroid, leiomyoma, OHPC, MPA, Provera, AUB

Introduction

Endometrial protection is the most problematic aspect of postmenopausal hormone replacement therapy (HRT, AKA Menopausal Hormone Therapy, MHT). While there are many safe and reliable means of restoring testosterone (T) and estradiol (E2) levels to premenopausal levels (commonly known as optimization-level therapy), doing so in intact women requires a P (progesterone/progestin/progestogen) component to prevent the elevated E2 levels from causing endometrial proliferation/hyperplasia. Oral synthetics such as medroxyprogesterone acetate (MPA/Provera), the most common prescription, have been shown to increase risk of blood clots, breast cancer, depression, and many other negative outcomes[1]. Oral micronized progesterone (OMP/Prometrium) causes debilitating side effects (grogginess, anxiety, depression, etc.) in most women notwithstanding its promotion by many prescribers as a sleep aid. OMP also offers poor endometrial protection[2], possibly due to underdosing in an attempt to minimize these side effects. OMP is especially likely to be problematic when levels are assessed with the most commonly used immunoassay blood serum test because that overestimates the level of protection[3]. Transdermal and especially transvaginal progesterone are more accurately assessed with standard testing (albeit not saliva tests[4]), but are often poorly tolerated due their burdensome application method or schedule (transdermal progesterone must be applied twice a day to provide stable levels due to its short half-life), and risks associated with transfer to pets/children/spouses.

This discrepancy is most pronounced in the best tolerated and longest-acting forms of HRT, pellets and injections. While T and E2 pellets need only be replenished after several months, and injections (of the prohormones testosterone cypionate (T-cyp) and estradiol cypionate (E-cyp)) once or twice a week, there is no viable pellet form of progesterone (the volume of such a pellet would be prohibitive) and bioidentical progesterone injections would need to be injected every day due to its short half-life. As a result, side-effect inducing doses of OMP are most commonly used with these protocols.

There is unfortunately no prohormone of progesterone that is metabolized comparable to the way T-cyp and E-cyp are, the first step in their metabolism being snipping off the cypionate ester leaving the bioidentical hormone to continue activating receptors and to register on standard lab tests. But an extensive review of progestins available in the US turned up something comparable at least in structure: 17-hydroxyprogesterone caproate (OHPC aka Makena/Delalutin), a bioidentical form of progesterone with an ester attached. Besides having a half-life comparable to T-cyp and E-cyp, OHPC has the additional advantage of having a very low affinity for glucocorticoid receptors[5] such that it has little or no impact on mood and a lower likelihood of causing blood clots as has been associated with other synthetics. Although OHPC is used in the US primarily for pregnancy support for women at risk for pre-term labor and delivery, it had been used in a variety of other applications as Delalutin and Prolution prior to that being withdrawn from the market in the late 1990s due to poor sales, longer acting MPA (as Depo-Provera) having captured the majority of the contraceptive market. Notably OHPC is still used (with estradiol valerate) as a once-monthly injectable contraceptive in Central America and in China where it is known as Chinese Injectable (or Needle) No. 1.

Method

Participant was an Asian female age 62, 10 years postmenopausal, who had not previously been on HRT: Her perimenopausal phase coincided with the peak of the anti-HRT coverage in the popular media following the early termination of the WHI study. Full written informed consent was obtained from the participant to present her case and she possessed considerable knowledge of the alternatives and had a strong bias against the oral and synthetic hormones used in conventional HRT. A family history of CVD justified her bias against MPA (Provera) and oral estrogens, both of which the WHI convincingly showed increased these risks[6], although her 0 score on a Coronary Artery Calcium (CAC) scan indicated the primary concern was blood clots, not elevated lipid levels that could cause atherosclerosis. We and the participant furthermore discounted guidelines recommending HRT only within 10 years of menopause because those are based on the assumption that E1-based treatments (Premarin/CEE and oral estradiol) have identical physiological effects to E2-based treatments, an assumption that has been shown to be false[7].

Her intake questionnaire showed that her symptoms included loss of libido, vaginal dryness, hair loss, cold extremities, sarcopenia, and weight gain. She had been prescribed a bisphosphonate to address osteopenia but which was poorly tolerated. Labs indicated multiple nutrient and hormone deficiencies. OTC supplements were recommended to address the vitamin and mineral deficiencies, and NDT (Nature-throid and later NP Thyroid plus Cytomel (liothyronine)) prescribed to address her subclinical hypothyroidism. The sex hormone protocol for the first 3 months was T-cyp and E-cyp by twice-weekly injection with OMP 150mg taken each evening. Although the T-cyp and E-cyp were effective and well tolerated, OMP was poorly tolerated (grogginess that persisted until afternoon the next day) and only raised serum P levels to about 3ng/ml (measured 12 hours after the dose with the standard (albeit inappropriate) immunoassay test), well short of the generally accepted minimum of 5ng/ml required for endometrial protection[8].

Target level for E2 were 90pg/ml (the median E2 level in premenopausal women). Achieving this required 1.35mg of E-cyp/wk (0.27ml of 5mg/ml) for the 110lb (50kg) participant, noting that doses should be scaled by body weight. This also pushed her FSH down from 119 to 3.6, just below the median level in premenopausal women. The target T level was the top of the lab range for Free Testosterone (4-5 for the Labcorp “Free Direct” tests) which required 18mg per week (0.09ml at 200mg/ml). Adjusting dosing of T and E2 was straightforward: A blood test performed after 4 weeks on the protocol allowed calculating the dose to achieve target levels with a high degree of accuracy, and because E2 was supplemented directly this protocol does not require the overdosing typical of testosterone-only pellet-based therapy[9]. This weekly adjustability means that injections are generally free from the serious consequences of unintentional extreme overdoses that also occasionally occur with pellets.

To replace the OMP we chose target level of OHPC equivalent to a progesterone level of 10ng/ml. Although published reports claim that OHPC and progesterone are roughly equivalent in efficacy on a mg/mg basis[5], building in a little extra protection beyond the 5ng/ml required for endometrial protection seemed prudent given that many these reports are not based on data from postmenopausal women. 10mg/ml also happens to be closer to median levels found in nursing women, who also require robust

endometrial suppression (as a natural form of birth control). Because OHPC does not show up on standard labs we calculated dosing based on published dose-response reports[11]. This calculated dose was 135mg/wk (0.54ml at 250mg/ml), just over half the therapeutic dose for pregnancy support. Note that all three of these compounds are FDA approved, but OHPC and T-cyp are off-label for HRT and in women, respectively. The T-cyp and E-cyp used were in factory-produced vials available from any pharmacy at reasonable cost whereas OHPC is only available at reasonable cost from compounding pharmacies (approximately $80 USD for a 10ml/2500mg vial): Factory produced OHPC (Makena) costs approximately $600 per 250mg autoinjector and is not available through retail pharmacies.

The three injectables were combined into new empty sterile vials at a 6:3:1 ratio of OHPC:E-cyp:T-cyp at the specified concentrations: 250mg/ml, 5mg/ml, and 200mg/ml, respectively. 0.4ml of this mixture was injected SC into a fat pad on the belly or upper buttock Monday morning and Thursday evening. The smaller volume in this split dose is significant: Larger injections would be significantly more likely to cause issues at the injection site.

Results

Serum testing at trough levels (at the day and time of a scheduled injection, before that injection) confirmed that target levels of E2 and T were achieved and maintained. Ultrasound taken after 3 months on OHPC showed the effects of the previous 3 months under-opposed estrogen treatment: Endometrial stripe was 5.4mm and a 2.4x2.4x2.5cm (asymptomatic) fibroid was reported. After 9 months of OHPC the stripe was reduced to an optimal 4mm thickness and that fibroid was reduced to 1.7x1.6x1.5cm, a 70% reduction in volume. After an additional 11 months the stripe was 3mm and the fibroid had been reduced to non-significance and then to non-detectability. As the suboptimal stripe thickness indicated overtreatment with OHPC, the ratio was changed to 5:4:1 and the dose reduced to 0.35ml, resulting in a weekly dose of 87.5mg OHPC, 1.4mg E-cyp, and 14mg T-cyp. There has never been any sign of spotting or bleeding after 5 years on this protocol..

The protocol was well tolerated by the participant who noted significant improvements in mood, strength, libido, quality of skin and hair, and sleep. The post-treatment questionnaire indicated that all of the symptoms prior to HRT were largely to completely eliminated. The prescription drug for osteopenia was discontinued due to the estradiol being protective without the side effects. Other than occasional “stingers” at an injection site that passed as soon as that injection was finished there were no adverse reactions. There were also no significant side effects although a slight increase in acne and body hair growth (comparable to what she experienced in her 20s) was noted. Cost was cited as another significant benefit: Including shipping from an mail-order compounding pharmacy and supplies the total cost of this protocol was less than $50 a month, less than 1/3 the cost of pellets or best available pricing on Prempro. This is a critical difference for many women because most health insurance plans do not cover optimization-level HRT.

Discussion

Self-administered injections is by far the most common mode of Testosterone Replacement Therapy (TRT) in the US (used 3:1 over pellets[10]), yet are rarely considered for HRT in women. This study shows

that not only is this mode viable for women, but can be much better tolerated and much less expensive than the alternatives. The reduction in fibroid volume was an unexpected benefit: Many progestins, notably MPA, have been shown to increase the size of fibroids and so if they are used in HRT it has been recommended that low doses be used to minimize fibroid growth[12] or that SERMs be used instead[13]. But the fibroid reduction in this case is far larger than any previously reported in the literature for any other progestin or SERM.

Conclusion

OHPC is clearly worth another look, not only for HRT but also as an alternative to D&C/ablation/hysterectomy as a treatment for abnormal uterine bleeding (AUB), and to myomectomy for symptomatic fibroids. Although there have been no reports of negative effects from long-term use of OHPC even among Chinese women using it for contraception, it has not been widely used for HRT and so close monitoring of patients using it for that purpose is warranted. The main limitation of this study is that it is a case report and cannot be generalized at this point, but there is reason for optimism that further studies will support this novel treatment for endometrial protection in post-menopausal hormone therapy. In addition to further establishing the safety of this protocol, a larger study also would enable investigation of OHPC dose sizing since we have determined our initial dose larger than necessary.

Data Availability

Three ultrasound reports documenting endometrial thickness and reduction of fibroid and the corresponding scans are available upon request from the corresponding author.

Conflicts of Interest

None.

Funding Statement

None.

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Appendix 1: Reviewer comments and author's responses

> This paper is well-written and researched. It poses an interesting question which likely warrants more investigation as HT regimens can be difficult to adequately manage and often not well-tolerated by patients.

> The reduction in fibroid size is potentially very interesting. I am not sure I would classify a 2cm asymptomatic fibroid as large. May want to describe it in other ways.

> More discussion is needed on limitations of the proposed intervention and selected patient. What are potential pitfalls in a more broad population?

Nowhere in the paper was the fibroid described as "large". 3cm is typically described as medium sized (excuse me for rounding up from 2.5cm). This is not about large populations, it's a Case Study and as such is *automatically* assumed to include these disclaimers about general applicability. I.e., that's for a future controlled study to answer.

> How many patients can easily access compounding pharmacies? This is an issue for many pregnant women, especially those from lower socioeconomic backgrounds or who are under/uninsured.

Products were supplied by mail order compounding pharmacies. All Americans have access to these, and the price per month is quite reasonable even for the under or uninsured as it is competitive with other HRT protocols.

> Please also provide discussion regarding futures (sic) directions for investigating this intervention.

This is a Case Study so future directions is not relevant (again, until somebody runs a controlled experiment).

> Please elaborate on your mention of research using social media platforms. Many pitfalls can occur in a potentially very biased setting such as a group social media platform

This comment discloses a profound ignorance of what's going on out here in the real world. Real scientists *can* get useful information from social media, and using social media to collect anecdotal reports does not mean you are not a real scientist.

> For the supplemental material - While this will not be published with the article the items should appear cleaner. A scanned ultrasound report does not seem necessary.

Using the actual printed report rather than editing raw data files preserves authenticity, even if we had access to the radiologists hard disk. Which we didn't. Nor is this relevant to the quality of the paper

> I would recommend removing extraneous information off of the ultrasound images. The hospital/health system information does not need to be on the images.

Again, not relevant to the publishability of the paper.

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> The authors employ a hydroxyprogesterone caproate (OHPC) as a progestin in menopausal hormone therapy (MHT). In a single patient they noted appropriate endometrial suppression with the added effect of fibroid volume reduction.
>
> I have several concerns about your case report:
>
> 1. Did you receive IRB approval for this case usage of OHPC?

This is disclosed in the cover letter: There was no IRB as this is a private practice.

> 2. The descriptions of the side effects of MPA, transdermal P and oral micronized progestin are greatly exaggerated. Please include percentage of patients that developed the side effects that you claimed. Many of these are theoretical, yet to be proven and are not based on RCTs. One of the reasons we do not see side effects related to OHPC is due to its limited use and thus hindered by small sample size.

This just exposes a profound ignorance of the last 20 years of research on HRT. It's like they never heard of the WHI. OHPC *is* used by millions of women in China and Central America and was widely used in the US prior to the development of MPA/Provera and other oral progestins. There has been no reports in any of these to suggest that OHPC has anywhere near the risk profile of MPA, which *has* been widely reported.

> 3. I am surprised you use compounded OHPC. Commercially available OHPC (cost $400 to 600 per 250mg) undergoes rigorous quality control analysis, thus assuring a consistent does. Although compound OHPC is inexpensive, it is known to have wide variation of quality and quantity of hormone. In our own experience we have seen very high levels of variation in the OHPC received from compounding pharmacies.

This comment is only relevant if the treatment had no effect or if there were other adverse events associated with it. These do not apply to this Case Study. The claim of "variation" furthermore is most likely false: While bogus products *have* been an issue in all sorts of drugs and hormones it's simply not an issue with larger compounding pharmacies (such as the mail-order pharmacies we used) that actually test their products. Claiming that paying a minimum of $800 a month for just one component of HRT is reasonable would be laughable if it didn't serve as a damning indictment of how out of touch doctors (and researchers) are.

> 4. Why was it necessary to adjust doses to strict measurements of hormone levels. This is unrealistic in patients on MHT. Based on patient's metabolism, absorption, binding proteins, inaccurate assays (especially free testosterone); the individual variation of estrogen, testosterone and progesterone/progestins levels vary widely. Measurement of these levels is

> futile, especially if one uses compounded OHPC . Did you consider measuring the person's lipid levels?

This just displays a profound ignorance of the state of the art in medical practice as of the 2020s. Levels on injections in particular are extremely stable, easily reproducible and adjustable, and measured with a high degree of accuracy by current lab tests. Lipids were measured and were unchanged, so your attempt to discredit T supplementation has failed.

> 5. Patient requires biopsy evidence that the hormone therapy was effective in suppressing endometrium. The ultrasound findings are not sufficient to demonstrate endometrial suppression especially in a (sic) experimental therapy.

That's just not how any of this works. It is not physiologically possible to maintain a 3-5mm endometrial stripe of proliferative endometrium, especially over a period of 5+ years.

> 6. I am disappointed in your over exaggeration of the results from the use of this in only one patient. You need to tone down your results considerably until you have a large randomized controlled trial.

It's a remarkable result. Pardon my enthusiasm. Based on an extensive survey of published Case Studies/Reports this type of "salesmanship" is standard in this genre.

> 7. Occasional fibroids are known to shrink quickly in the postmenopausal. How do you know this is not just the normal course of this fibroid versus to treatment.

Again, ignorance exposed: This does not ever happen in postmenopausal women on HRT. In fact the opposite is nearly always the case: Fibroids grow after shrinking in untreated perimenopause frequently leading to adverse outcomes.

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> Ln31: You described no effect on blood clot with OHPC, what is this based on?

It has not been reported as a side effect when OHPC is used for pregnancy support nor as a contraceptive.

> Ln41: What does the Women's Health initiative have to do with this case?

The WHI used MPA/Provera which has been shown to significantly increase the risk of clots and some cancers. It also increases the size of fibroids.

> Ln 46: I had challenge (sic) your assumption that HD should be use for greater than 10 years. The article you referenced (ref7) does not support your hypothesis. Please comment?

That paper *does* recommend the long term use of E2 vs. EE in women with POI. Which *is* my point. This 10 year thing has also been widely discredited elsewhere.

> Ln 52: What OTC medications were recommended for treatment of her thyroid disease?

The supplements were for vitamin and mineral deficiencies.

> Ln 54: Testosterone supplementation in postmenopausal females is controversial? Please comment on the safety of this medication.

It's not controversial in 2020 except among some reviewers who don't keep up with the literature or the state of the art practice of medicine.

> Ln 67: ".. Injections or gently free from serious consequences of unintentional extreme over doses.." What is the evidence for the basis of the statement? Was this based only on this 1 patient?

TRT is most commonly done by injection for men, and has been for decades. It's also more recently become common among women albeit only those who's doctors are keeping up with the state of the art in medical practice. The widely varying levels in pellet therapy is widely known and examples have been published in the peer-reviewed literature.

> Ln 96: Are you claiming this therapy improved osteopenia and can treat hypertension? Please comment?

This is a general benefit of HRT. There is no reason to believe that it's even theoretically possible that this protocol would not accrue those benefits.

> Discussion: You (sic) discussion makes many statements that are not proved by her single case. Thus you need to provide a more realistic outlook on the use of this medication.

It's a Case Study, not an FDA approval submission.

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> There are some major concerns regarding the manuscript.
> 1. The patient was not provided with an initial attempt at HRT to determine if symptom relief would be adequate and was switched directly to low dose injectable T-cypionate, E-cypionate, and 17OHprogesterone caproate.

This is irrelevant to the primary claim, which is that the protocol shrinks fibroids with no adverse side effects.

> 2. T, E2 levels were measured without respect to peak/trough pharmacokinetics.

Thisis irrelevant for weekly (or bi-weekly) administration of T-cyp, E-cyp, and OHPC by injection as levels fluctuate very little.

3. The author appears bias against conventional HRT and focuses on negative side effects of micronized progesterone and MPA. There is no mention of side effects of injectable T-cyp, E-cyp, or 17OH caproate.

Because there aren't any? Other than a slight increase in acne, there *were* no significant side effects in this case. Which is kind of the point.

4. The statement regarding transdermal estradiol excludes estradiol patches.

There is no statement about transdermal E2, only transdermal P. There is no bioidentical P patch.

5.The injectable compounds are not bioidentical.

Technically they are prohormones of the bioidentical and as such means this statement is intentionally misleading or just plain ignorant.

6.Additionally 17OH-progesterone caproate is not metabolically cleaved and is biologically active in its caproate form.

This is discussed.

Unfortunately, there is no new information presented by this case report.

A more ignorant statement has never been uttered by a reviewer, I'm sure, and the lack of concern for the plight of women with fibroids is also a strong indication of sociopathy. Who qualifies these reviewers?

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The case report presents the clinical outcome of a patient given injections of 0.4 ml twice weekly that contained 250 mg/ml hydroxyprogesterone caproate, 5 mg/ml estradiol cyprionate, and 200 mg/ml testosterone cypionate for menopausal symptoms. The author contends that the fixed dose formulation was designed to achieve physiological levels of progesterone, estradiol, and testosterone. Serum levels are not shown. The author reports that the patient noted an improvement in mood, strength, libido, sleep, and quality of skin and hair as well as a reduction in endometrial stripe and fibroid size. The fixed dose formulation has been dubbed Fail Proof Protocol. The supplemental data show the ultrasound reports but not images and also show the patient's and doctor's name raising concern about HIPPA

> compliance. There are no formal assessments of quality of life. The study reports an intervention but it does not appear that informed consent was obtained.

OK, full disclosure, the patient was in on it from the start! She even (horrors!) helped develop the protocol!

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> This is an interesting case report of hydroxyprogesterone caproate (OHPC) being successfully used in conjunction with HRT, which also led to fibroid reduction.
> Major comments
> - The submitted supplemental file having the patient's actual name is problematic. Please remove.

These were for the reviewers benefit and would not have been published anyway (so it doesn't matter).

> - Ideally the actual images of the ultrasound would be preferred than just the written report. Also please provide BOTH before and after treatment imaging, if available.

Images available upon request, but it's hard to show an image of a non-existent fibroid.

> - While the authors tout the potential of OHPC in certain circumstance and report that the 1 patient reported minor adverse effects, for a balanced consideration, it should be acknowledged in the discussion, if appropriate, that the long-term effects of OHPC are unknown, and the tone of the discussion a bit more cautious. If there is literature that addresses potential adverse effects of OHPC, particularly long-term effects, then this should be added in the discussion.

There is literature on safety and adverse effects. The PDR has this in English, but the long-term data is all in Spanish or Chinese (as reported in the paper) or merely reflected in Standard of Care practices in these countries. Again, this is not relevant to whether or not the paper is a useful Case Study and omitting it only would be a problem if this were a controlled study that was intended to be used to modify Standard of Care directly.