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TITLE: A Pharmacokinetic/Pharmacodynamic Study of the Glucocorticoid Receptor Antagonist Mifepristone Combined with Enzalutamide in Castrate-Resistant Prostate Cancer

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14. ABSTRACT

This is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor (GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The first objective is, within the context of a phase I clinical trial, to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. During this funding period, the phase I was completed and randomized phase II portion initiated. Thus far the combination of mifepristone and enzalutamide has been well tolerated with no dose limiting toxicities. During this period, agreement with contract execution for enzalutamide to be provided free of cost was reached with Astellas; this will greatly facilitate accrual. During the next year, the goal is to accrue to the phase II with addition of three other external sites to augment accrual.

15. SUBJECT TERMS
Castration resistant prostate cancer (CRPC); Androgen Receptor (AR); Glucocorticoid receptor (GR); Enzalutamide; Mifepristone; Pharmacokinetic (PK) Pharmacodynamic (PD); Prostate specific antigen (PSA)

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1 INTRODUCTION:

This award is a Clinical Exploration Award funding a clinical trial for patients with metastatic, castration resistant prostate cancer (CRPC). For patients with metastatic CRPC, there are few established therapeutic options and the prognosis remains dire. The overarching goal of this translational research award is to build on concept that under the selective pressure of androgen receptor (AR) targeted therapies, prostate cancer adapts. One way it adapts is by upregulating another hormone receptor, the glucocorticoid receptor GR), which may compensate for diminished AR activity. The clinical trial within this award is a phase I/II clinical trial of the GR antagonist mifepristone in combination with the FDA-approved AR antagonist enzalutamide. The two major objectives of the award correspond to the two phases of the trial that will be articulated in more detail within the "Accomplishments" section of the report. The first objective is within the context of a phase I clinical trial to establish safe and pharmacologically active doses of the two drugs for use in combination for daily dosing. This will be completed at the lead site. The second objective is to use pharmacodynamic biomarkers to support the hypothesis that GR antagonism in combination with AR antagonism will delay CRPC progression. This portion of the study will be a multiple-institutions study, lead by the lead site.

2 KEYWORDS

The following are key words that will be used in this report
Castration resistant prostate cancer (CRPC)
Androgen Receptor (AR)
Glucocorticoid receptor (GR)
Enzalutamide
Mifepristone
Pharmacokinetic (PK)
Pharmacodynamic (PD)
Prostate specific antigen (PSA)

3 ACCOMPLISHMENTS:

A. What were the major goals of the project?

Please note that a revised statement of work (SOW) was submitted and approved 11/2015 as was a no-cost extension allowing for 48 month study duration.

As stated in the revised SOW, the major tasks for the study, with projected timeline are listed as follows. Specific activities accomplished, in concordance with SOW during this quarter will be detailed in the next section.

Major Task 1: Regulatory Approval: Lead and subsidiary sites	**Months 1-30**
Major Task 2: Coordinate and Initiate Phase I Portion of Study	**Months 1-9**
Major Task 3: Complete phase I study	**Months 1-27**
Major Task 4: Initiation of Phase II	**Months 25-30**
Major Task 5: Complete Phase II study	**Months 27-48**
Major Task 6: Data Analysis	**Months 27-48**

B. What was accomplished under these goals?

The following tables summarize the objectives/subtasks to be accomplished during this reporting period specifically, with comments when pertinent.

Major Task 1: Regulatory Approval: Lead and subsidiary sites			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Subtask 1: Obtain Regulatory Approval for Research Protocol at UC: COMPLETE			
Subtask 2: Obtain Regulatory Approval for Research Protocol at PCCTC sites			
PCCTC site identification		Partial	As per the initial award and budget, three external sites can be included. Although there was enthusiasm from Duke, they could not open internally due to financial limitations of this award. The trial will be opening at NorthShore University (D. Shevrin PI) and is being reviewed at Karmanos Cancer Center (Heath) and University of Washington in Seattle (Higano). Northwestern and Illinois Cancer Care will be next sites as backups if any of the above fall through.
Scientific and IRB submission at PCCTC sites	25-28	Partial	Regulatory documents sent to sites above
Coordination of Clinical Trials Agreement (CTA) at PCCTC sites	25-28	Partial	Active central CTA agreements are already in place between the University of Chicago and PCCTC sites as well as University of Chicago and
Scientific Review Approval PCCTC sites	25-28	No	See abovc
IRB Approval PCCTC Sites	25-30	No	See above

Major Task 2: Coordinate and Initiate Phase I Portion of Study			
	Timeline (months)	**Objective complete**	**Findings, developments, discussion points**
Finalization of data capture forms	1-3	Yes	
Site initiation training at UC	1-3	Yes	
Screening and Registration of first patient on phase I at UC	1-3	Yes	

Major Task 3: Complete phase I study	Timeline (months)	Objective complete	Findings, developments, discussion points
Recruitment and enrolment	1-24	Yes	See below
PK analysis	3-27	Yes	See below
Weekly institutional data safety monitoring board	1-36	Yes	Ongoing

Monthly safety/oversight teleconference	27-48	NA	Will begin with multi-site participation
Submission of year 1 IND report to FDA	9-12	Yes	Year 2 IND report also submitted
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	Personnel and minor clarification amendments submitted to IRB. No significant changes that mandated HRPO submission
Milestone Achieved: Completion of phase I study	9-12	Yes	

Major Task 4: Initiation of Phase II			
	Timeline (months)	**Objective Complete**	**Findings, developments, discussion points**
Finalize Recommended phase II dose	25-27	Yes	Phase II dose was determined based on phase I to be enzalutamide 120mg and mifepristone 300mg, both daily
Finalize Data Capture forms for phase II **	9-12	Yes	
Orientation and training of sites for phase II trial	25-27	No	See above. When at local IRB, will do site initiation
First patient randomized on phase II trial	27-30	Yes	

Major Task 5: Complete Phase II study			
	Timeline (months)	**Objective Complete**	**Findings, developments, discussion points**
Recruitment and enrolment	27-48	Ongoing	TBD
Data Capture and Input	15-48	Ongoing	TBD
PK analysis (Batched for Phase II portion of study)	33-48	Ongoing	PK Samples will be collected and batch analyzed at end of accrual
Weekly institutional data safety monitoring board	25-48	Ongoing	Weekly DSM
Monthly safety/oversight teleconference	25-48	Ongoing	Teleconference for external sites is set up and other sites will join when open
Submission of year 2 IND report to FDA	21-24	Yes	
Submission of year 3 IND report to FDA	33-36	No	Not due yet
Submission of any protocol amendments to IRB, FDA, HRPO	Continuous	Yes	

***Note: No items within SOW to be completed on task 6 during this reporting period**

Discussion of Accomplishments:

Within this reporting period (year 3) the primary task has been to completion the phase I portion of the study and initiation of the phase II. Due to the 60 day DLT periods and more dosing

cohorts needed then initially anticipated, as well as commercial enzalutamide supply hurdles, this has taken longer then anticipated. Phase I is now complete. There were no dose limiting toxicities, however one patient did come off study electively during the DLT period for grade 2 fatigue and memory changes. These are anticipated side effects of the two study drugs. We continue discussing the study weekly at our data safety monitoring meeting, and with our independent trial monitor, including a discussion of potential subjects available for recruitment. In addition, as the protocol is an investigator initiated trial and the University of Chicago has intellectual property involving the underlying concept of dual GR and AR blockade, over the last reporting period, as suggested by the University of Chicago IRB, the protocol is now being reviewed for safety and data integrity at the University of Chicago Comprehensive Cancer Center High Risk Clinical Trial committee. This committee meets quarterly and last met 12/9/16 with no issues reported.

Task 2 is complete with no details to report. Data capture of enrolled patients at the University of Chicago is ongoing without issue. Task 3 is centers around completion of the Phase I clinical trial as described above and has been completed since last yearly report.

The phase I data is as follows:

Table 1. Patient Demographics

	40mg	*80mg*	*120mg*
N	6	6	6
Ave age	73	72.	68.
Baseline PSA (median)	13.1	54.3	171.3
Baseline PSA (range)	1.53-34.3	4.74-101.8	2.89-255.6
Caucasian (%)	66	50	83
African American (%)	33	50	17

The age and ethnic background is well balanced and consistent with our prostate cancer population as a whole. Of note, cohort three had a substantially higher baseline starting PSA as a cohort. Enzalutamide is the FDA approved backbone of this trial. Due to safety and PK concerns, the dose of enzalutamide was started low at ¼ dose (40mg) and has been escalated first to 80mg and finally to 120mg daily; each cohort with 300mg mifepristone. The results of this cohort were reported in last year's report. The second cohort was 80mg enzalutamide and 300mg mifepristone. The PK ratio for this cohort was 0.70 (70%), with 0.75-1.5 being acceptable for phase II. Cohort #3 was dosed at 120mg/day enzalutamide with 300mg/day mifepristone. The average PK ratio's for day 57/Day 29 for cohort #3 (ř) was 1.02 (Standard deviation 0.2, range 0.78-1.36). There have been no DLT through the first 18 patients. The two drugs in combination have been well tolerated, with the most common side effect being fatigue (1 grade 3, not in DLT period, 6 other patients with grade 2). There have been no new safety events since last yearly report. See table 2 for summary of AE's reported grade 2 or higher deemed potentially study drug(s) related.

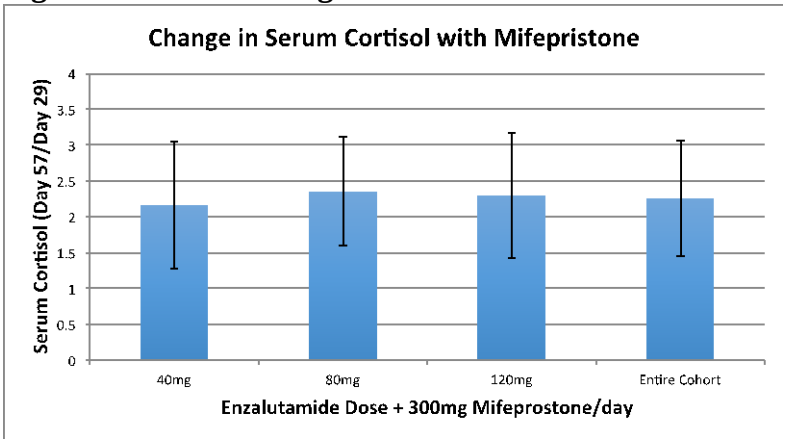
Table 2. Cumulative Adverse events to date, grade 2 or higher, potentially related

Adverse Event	*Grade 2 (n,%)*	*Grade 3 (n,%)*
Agitation	2, 11	
Amnesia	1, 5.5	
Arthralgia	1, 5.5	

Confusion/Cog dec	**1, 5.5**	**1, 5.5**
Depression	1, 5.5	
Dysphagia		**1, 5.5**
Fatigue	**7, 38.9**	**1, 5.5**
Gynecomastia	1, 5.5	
Hot Flashes	2, 14.3	
Hypoglycemia	1, 11	
Insomnia	1, 5.5	
Myalgia	1, 5.5	
Nausea	2, 11	
Pain	1, 5.5	
Pneumonitis	1, 5.5	
Rash	1, 5.5	
Urinary Incontinence	1, 5.5	

From a PD standpoint, serum cortisol levels were measured before and after mifepristone at 300mg. Cortisol routinely doubled as expected, indicated on target GR antagonism. The per cohort change in cortisol is displayed graphically in Figure 1. It was therefore deemed that 300mg mifepristone is sufficient GR antagonism and no further dose escalation of mifepristone was indicated

Figure 1. Cortisol change for Phase I



With respect to efficacy, enzalutamide+mifepristone has lowered PSA as anticipated (Figure 2).

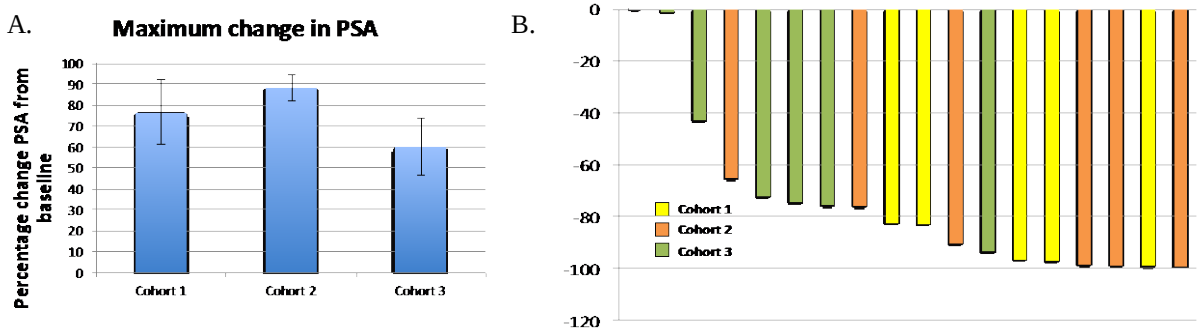
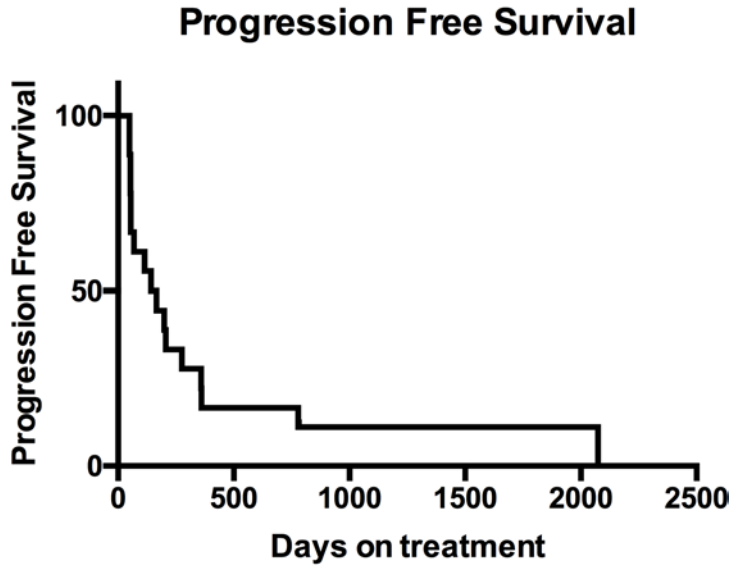


Figure 2. PSA Change During Phase I Portion of the Study. A. Per dosing cohort average change in PSA +/- standard deviation. B. PSA waterfall plot showing maximal change in PSA.

Progression free survival (PFS) for the entire cohort to date is shown in Figure 2. Median PFS is 276 day (9.8 28 day cycles), which is in line with reported PFS in phase III study of enzalutamide (8.3 months, Scher et al, *New England Journal of Medicine*, 2012).

Figure 3. Progression Free Survival for Phase I Population



Based on PK, which was very consistent and lack of any safety concern in any cohort, decision was made to proceed with phase II randomized portion of the trial.

It was noted that a very significant barrier to enrollment was the change in medication approval landscape over the last 2 years. Specifically, enzalutamide, as a very expensive medication, was no longer being approved by insurance carriers or was approved but with thousands of dollars/month in patient copays. As such, the PI has re-submitted the study to Astellas/Medivation, manufacturer of enzalutamide. It was approved by Medivation/Astellas nationally in early 2016 and global Astellas leaderhip approved mid 2016. This then resulted in another ~4 months of contract negotiation. The study accrual was on hold for ~6 months during this period. Contracts with both Astellas and Corcept Therapeutics were executed in November 2016. Three patients have since enrolled, with 2 additional in screening and 2 who signed consent but did not proceed on study (one withdrew consent to pursue chemotherapy and one screen failed due to insurance refusal). Thus, accrual is now unhindered and picking up. As noted above, 3 other sites are moving the study through their processes in effort to open in Q1 2017.

C. What opportunities for training and professional development has the project provided?

This award was not intended for professional development as it is not a training award. Nonetheless, the trial has allowed the PI, a junior investigator, to work as a lead investigator on a complex, multi-site clinical trial. As such provided the PI an opportunity to present trial progress at the PCCTC semi-annual meetings as well as present and participate in monthly teleconference. The PCCTC meetings are attended by representatives from ~15 leading prostate cancer research institutions and included

multiple thought leaders in the field. The PI was able to share trial progress and garner support in the group for the trial, which was an excellent learning opportunity.

D. How were the results disseminated to communities of interest?
There were no results to report during this reporting period. However, an abstract poster was presented at the largest international oncology meeting, the ASCO national meeting, within the Trials in Progress session. This poster was very well received.

E. What do you plan to do during the next reporting period to accomplish the goals?
The principal goal during the next reporting period is to continue enrollment for the phase II trial. This will include opening at 3 other sites. It is likely that enrollment will proceed for 2 years.

4. IMPACT:

A. What was the impact on the development of the principal discipline(s) of the project?
The clinical trial has not completed and we do not have full results. Therefore, there are no significant impacts to the prostate cancer field as of yet. However, one key impact is that our trial is the first to our knowledge of enzalutamide in combination with another drug that is a pharmacologic inhibitor of enzalutamide metabolism. Enzalutamide metabolism is complex and involved multiple hepatic enzymes. We have shown that a strong inhibitor of CYP2C8/9 and CY3A4 essentially decreases clearance of enzalutamide by half. Beyond our trial, these data may have an impact as enzalutamide is considered in combination with other drugs.

Specifically, the University of Chicago and Northwestern are partners on a NIH SPORE in Prostate Cancer Award, which began in the last year. The PI of this DOD award was awarded a Major Project grant within this SPORE to further interrogate GR and AR. This will include a clinical trial with a novel GR antagonist with enzalutamide. The trial design for this trial, supported by the NIH SPORE, was informed by the PK data from this award.

B. What was the impact on other disciplines?
This study is the first study of mifepristone at 300mg daily dosing in an advanced cancer population. GR antagonism is a potential therapeutic maneuver for other cancers, such as breast cancer. We have shown that daily dosing of mifepristone in patients with advanced cancer is safe. This is impactful as the knowledge of its safety in this population can be used as the drug is developed in other cancers.

C. What was the impact on technology transfer?
The University of Chicago was granted a US patent on the concept of dual AR and GR antagonism based on preclinical work, which was licensed to Corcept Therapeutics, in part due to enthusiasm surrounding this currently ongoing clinical trial.

D. What was the impact on society beyond science and technology?
Nothing to report

5. CHANGES/PROBLEMS:

A. Changes in approach and reasons for change

There have been no changes in approach to this research award.

B. Actual or anticipated problems or delays and actions or plans to resolve them

It should be noted that there were barriers to fully accomplishing Major Task 3 prior to this reporting period. Accrual to the trial was slower then anticipated. We initially had a verbal agreement with Medivation who were to supply enzalutamide for this trial (Mifepristone is being supplied by Corcept Therapeutics). Rights to enzalutamide in the United States were sold to Astellas, and Astellas refused to provide enzalutamide for the trial. Although the FDA label for enzalutamide includes such dose reduction for use in combination with other medications that may inhibit enzalutamide metabolism, Astellas was not willing to assist our trial. As an alternative to enzalutamide being provided by Medivation/Astellas, patients enrolled on the trial, but get enzalutamide through their commercial pharmacy. This slowed accrual as prior authorizations are required and there is often a very high cost to the drug, even with insurance, that has somewhat limited the patient population eligible for the drug. For the phase II study this was resolved by contracting with Astellas/Medivation for free enzalutamide for patients enrolling on the phase II portion of the trial. This approval and associated contracting for this change took nearly 9 months, despite all efforts by the PI and his team. This will no longer be a barrier going forward.

Accrual was also held for ~4 weeks twice for PK analyses per protocol. There are not any further accrual holds planned for this study as it is in the Phase II portion.

C. Changes that had a significant impact on expenditures

Due to slower then anticipated progress in completing the phase I study, the phase II has only recently started. This delay will push back completion of the research project. As such, a no-cost extension has been granted for a fourth year of research. It is likely that a further no cost extension will be needed depending on accrual. *Accrual will be monitored during the first 2 quarters of 2017 and further adjustments to SOM, with associated no cost extension, will be submitted if appropriate.*

From an expenditure standpoint, all expenditures budgeted for outside site accruals have been separated from the internal University of Chicago operating budget and will not be affected by the extension. The extension will affect salary support for the PI and study personnel as there is not a budget for these salaries for a fourth year. In the fourth year and beyond, salary support will therefore be provided through internal funds. This has been discussed with and agreed upon by the Section Chief, and senior co-Investigator on this study, Dr. Stadler. There is no expenditure changes otherwise.

D. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: Nothing to report. The change to allow free drug rather then commercial supply does not change human subject risk, but will be submitted to HRPO by years end as summary of changes.

E. Significant changes in use or care of human subjects: Nothing to report

F. Significant changes in use or care of vertebrate animals: Nothing to report

G. **Significant changes in use of biohazards and/or select agents:** Nothing to report

6. PRODUCTS:

A. **Publications, conference papers, and presentations:** Abstract on the trial, including PK results from phase I were reported at ASCO 2016, in poster, written abstract form.
http://meetinglibrary.asco.org/content/170508-176

B. **Website(s) or other Internet site(s):** Nothing to report
C. **Technologies or techniques:** Nothing to report
D. **Inventions, patent applications, and/or licenses:** Nothing to report
E. **Other Products:** Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

A. What individuals have worked on the project?

Key Study Personnel	Study Roles and Responsibilities	Nearest Person Month, source of funding
Name: Russell Szmulewitz, MD Affiliated Institution: University of Chicago	Study Role(s): Principal Investigator Responsibilities: Study oversight and conduct	2, University of Chicago internal funds
Name: Elia Martinez, RN, OCN Affiliated Institution: University of Chicago	Study Role(s): Research Nurse Responsibilities: Coordinates research activities for the patients on the study	2, University of Chicago internal funds
Name: Julie Gruczynski Affiliated Institution: University of Chicago	Study Role(s): Study Coordinator Responsibilities: Data manager for the study. Took over role from Jaclyn Peterson	2, University of Chicago internal funds
Name: Walter Stadler, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual, research activities and data analysis	0.5 month, University of Chicago internal funds
Name: Peter ODonnell, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Chadi Nabhan, MD Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with patient accrual	0
Name: Mark Ratain Affiliated Institution: University of Chicago	Study Role(s): Co-Investigator Responsibilities: Assist PI with data acquisition and analysis	0.5 month, University of Chicago internal funds
Name: Theodore Karrison, PhD Affiliated Institution: University of Chicago	Study Role(s): Biostatistician Responsibilities: Generation of randomization algorithm and assistance with data analysis	1, University of Chicago internal funds

Name: Amanda Spratt, CCRP Affiliated Institution: University of Chicago	Study Role(s): Independent Safety Monitor Responsibilities: Oversee study accuracy of interventions, adherence to protocol guidelines, review study recruitment and the weekly data safety monitoring minutes for the trial and coordinate/oversee review of data matching and data collection across the trial. Member of the University of Chicago High Risk Protocol Committee, where this study is reviewed quarterly.	1, University of Chicago internal funds
Name: Daniel Bennett Affiliated Institution: InVentiv Health	Study Role(s): Pharmacokinetic laboratory supervisor Responsibilities: oversight and analysis of pharmacokinetic laboratory studies (does not have access to patient identifying information)	1, Medivation Inc

B. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

C. What other organizations were involved as partners?
Inventive Health, Inc. is a central laboratory that we have contracted with that is performing the PK analyses embedded within this trial. It is a fee for service agreement with the cost of the analysis being supported through Medivation Inc (Pharmaceutical Company that manufactures enzalutamide).

1. Organization Name: InVentiv Inc.
2. Location of Organization: Princeton, NJ
3. Partner's contribution to the project
    a. Facilities: provide facilities for PK analysis
    b. Collaboration: Samples collected on the trial are sent to InVentiv, who then analyze the samples and provide a report of the enzalutamide and metabolite levels to the University of Chicago.
4. Organization Name: Medivation Inc.
5. Location of Organization: San Francisco, CA
6. Partner's contribution to the project
    a. Financial: provide financial support for PK analysis

8. SPECIAL REPORTING REQUIREMENTS
None

9. APPENDICES
None