NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Novel hormonal therapies (NHTs) for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) in the Medicare population
Protocol number	C3431049
Protocol version identifier	4.0
Date	04 November 2024
Active substance	ATC: L02BB04, enzalutamide
Medicinal product	Xtandi® (enzalutamide)
Research question and objectives	Primary 1. Describe treatment duration among patients initiating first-line treatment with NHT (abiraterone, apalutamide, or enzalutamide) for mCSPC Exploratory 1. CCI [redacted] 2. Describe time to next therapy for patients initiating first-line treatment with NHT for mCSPC CCI [redacted] 3. Describe adherence for patients initiating

	first-line treatment with NHT for mCSPC CCI [redacted] 4. Describe baseline characteristics (including demographics, disease characteristics, prostate cancer history, comorbidities, and resource use) overall for patients initiating first-line treatment with NHT and compare them across treatment cohorts 5. Describe next treatment received among the overall cohort of patients initiating first-line treatment with NHT for mCSPC and separately for patients with first-line treatment with abiraterone, apalutamide, or enzalutamide CCI [redacted]
Authors	PPD MA PPD – Xtandi NIS Lead Pfizer Inc. 66 Hudson Blvd E New York, NY 10001

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADT	Androgen deprivation therapy
AE	Adverse event
ANOVA	Analysis of Variance
CI	Confidence Interval
CMS	Center for Medicare and Medicaid Services
CPT	Current Procedural Terminology
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
IEC	Independent ethics committee
IRB	Institutional review board
mCSPC	Metastatic castration-sensitive prostate cancer
NDC	National Drug Code
NHT	Novel hormonal therapy
PARP	Poly adenosine diphosphate-ribose polymerase
PDC	Proportion of days covered
PH	Proportional hazard

Abbreviation	Definition
US	United States
VRDC	Virtual Research Data Center

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Jasmina Ivanova, MA	Senior Director, Value & Evidence – Xtandi NIS Lead	Pfizer, Inc.	66 Hudson Blvd E, New York, NY 10001
Matthew Davis, MA	Principal	Medicus Economics, LLC	2 Stonehill Ln, Milton, MA 02186
Andrew J. Epstein, PhD	Principal	Medicus Economics, LLC	2 Stonehill Ln, Milton, MA 02186

4. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type(substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	04 August 2023	Substantial	Title page Section 7 Section 8.7	The primary objective was changed from comparison of duration of therapy between enzalutamide and abiraterone to a descriptive analysis of duration of therapy with first-line novel hormonal therapy (NHT; abiraterone, apalutamide, or enzalutamide) in metastatic castration-sensitive prostate cancer (mCSPC). CCI [redacted]	The primary objective was changed to a descriptive analysis of duration of therapy with first-line NHT because of uncertainty about adequate sample size and availability of sufficient follow up for product specific comparison of duration of therapy.
2.0	04 August 2023	Administrative	Title page	Title changed to "Novel hormonal therapies (NHTs) for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) in the Medicare population".	Change to reflect amendment to primary objective.
2.0	04 August 2023	Administrative	Section 5	Amendments to timelines to reflect new expected study start and timeline.	Updates to reflect new expected study start and timeline.
2.0	04 August 2023	Administrative	Sections 8.1, 8.2, 8.3, 8.4, 8.5, and 8.9	Clarifying that the end of index identification period will be on 31 December 2020 or 1 year before end of data availability. Clarifying that the end of data availability at present is 31 December 2021.	Update to allow use of more recent data if available (eg, data through 2022).
2.0	04 August 2023	Administrative	Section 8.7	Amendments to methods to reflect changes to primary and exploratory objectives.	Change to reflect amendments to primary and exploratory

Version Identifier	Date	Amendment Type(substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
					objectives.
2.0	04 August 2023	Administrative	Sections 9.1, 9.2	Updates to language for consistency with CT24 version 5 template for non-interventional study protocol template for secondary data collection study effective on 01 August 2023	Updates to align with version 5 of protocol template that became effective since initial protocol approval
2.0	04 August 2023	Administrative	Footnotes	Updated footnotes to reflect footnote in CT24 version 5 template for non-interventional study protocol template for secondary data collection study effective on 01 August 2023	Updates to align with version 5 of protocol template that became effective since initial protocol approval
3.0	05 January 2024	Administrative	Section 6	Deletion of a comma	Typo correction
3.0	05 January 2024	Substantial	Sections 8.1, 8.2, 8.2.1	Updated the start date of the index identification window to 01 January 2020	Start date of index identification window updated so that abiraterone, apalutamide, and enzalutamide were all approved for use in mCSPC
3.0	05 January 2024	Administrative	Sections 8.2 and 8.4	Updated study period start date	Update of the potential start date of baseline period to reflect the update to start date of index identification window
3.0	05 January 2024	Substantial	Section 8.2.2	Noted that patients with use of 1st generation antiandrogens 90 to 365 days before index date or within 28 days after index date will be excluded from the analyses	Ensure that patients' index NHT treatment is first-line treatment for mCSPC
3.0	05 January 2024	Administrative	Section 8.2.2	Exclude patients with use of lutetium Lu 177 vipivotide tetraxetan prior to index date or within 28 days after index date	Lutetium is only approved for use in mCRPC and its use may indicate that patients have mCRPC. As the approval was in

Version Identifier	Date	Amendment Type(substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
					2022, this change is not expected to impact the study population.
3.0	05 January 2024	Administrative	Section 8.2.3 Table 2	Added additional codes which may be used to identify treatments	Updates for completeness
3.0	05 January 2024	Administrative	Section 8.3 Table 3	Updates to baseline variables: -Clarification of definition of de novo mCSPC -Added baseline variable for long-term corticosteroid use and time from initial prostate cancer diagnosis to metastasis	Added baseline variables reported in other studies
4.0	04 November 2024	Substantial	Study information title page, Section 7	CCI [redacted]	
4.0	04 November 2024	Administrative	Section 8.1	Deleted "(at present 31 December 2021)"	At the time of analyses data were available through 2022
4.0	04 November 2024	Substantial	Section 8.3 Table 3	CCI [redacted]	
4.0	04 November 2024	Substantial	Section 8.4		
4.0	04 November 2024	Substantial	Section 8.7		

5. MILESTONES

Milestone	Planned Date
Start of data collection	10 September 2023
End of data collection	31 December 2024
Final study report	01 June 2025

6. RATIONALE AND BACKGROUND

Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the United States (US). The National Cancer Institute estimates 268,490 new cases and 34,500 deaths of prostate cancer in 2022.[1] While the long-term outlook is positive for early-stage prostate cancer, survival rates drastically decrease once the disease has spread beyond the prostate gland (ie, becoming metastatic) or when the disease becomes castration-resistant.[2]

Metastatic castration-sensitive prostate cancer (mCSPC) is a form of metastatic prostate cancer among men who have never received or are sensitive to androgen deprivation therapy (ADT).[3] The treatment landscape for mCSPC has evolved rapidly in recent years. Upfront intensified treatment with either docetaxel or novel hormonal therapy (NHT) added to a backbone of ADT has improved survival substantially.[4-7] The US Food and Drug Administration (FDA) has approved the NHTs abiraterone, apalutamide, enzalutamide, and most recently darolutamide in combination with docetaxel for the treatment of mCSPC in February 2018, September 2019, December 2019, and August 2022, respectively.

Outside of clinical trials, little real-world evidence exists regarding the amount of time that mCSPC patients spend on NHTs prior to discontinuation. The LATITUDE phase III clinical trial assessing abiraterone acetate + prednisone in newly diagnosed high-risk mCSPC patients found a median treatment duration of 25.8 months, while median treatment duration in the TITAN phase III clinical trial for apalutamide in mCSPC patients on ADT was 39.3 months.[9,10] Another phase III study in metastatic hormone-sensitive prostate cancer, ARCHES, found a median treatment duration of 40.2 months for enzalutamide plus ADT, and that earlier initiation was associated with improved outcomes.[6] These trials did not focus on directly comparing treatment duration across NHTs and evidence on how this may vary in real world applications is needed. In addition to time on treatment, research on real-world adherence to NHTs is limited by the fact that most of the published literature focuses on metastatic castration-resistant prostate cancer or more broadly on advanced prostate cancer.[11,12] There are no known studies specifically assessing real-world NHT treatment adherence for mCSPC.

Given that 60% of incident prostate cancer cases are diagnosed in men who are at least 65 years old and that Medicare is the predominant insurer among people aged 65+, Medicare is a key player for prostate cancer treatment.[13] Among the more than 61 million individuals enrolled in Medicare in 2019, 63% were enrolled in Original Medicare (while 37% were enrolled in Medicare Advantage) according to Center for Medicare and Medicaid Services (CMS) statistics.[14]

As there is an absence of published studies on NHT treatment adherence for mCSPC, this study seeks to fill that gap using administrative claims data from Fee-For-Service Medicare.

7. RESEARCH QUESTION AND OBJECTIVES

The study objectives are the following:

Primary

1. Describe treatment duration among patients initiating first-line treatment with NHT (abiraterone, apalutamide, or enzalutamide) for mCSPC.

Exploratory

1. CCI [redacted]
2. Describe time to next therapy for patients initiating first-line treatment with NHT for mCSPC CCI [redacted]
3. Describe adherence for patients initiating first-line treatment with NHT for mCSPC CCI [redacted]
4. Describe baseline characteristics (including demographics, disease characteristics, prostate cancer history, comorbidities, and resource use) overall for patients initiating first-line treatment with NHT and compare them across treatment cohorts.
5. Describe the next treatment received among the overall cohort of patients initiating first-line treatment with NHT for mCSPC and separately for patients with first-line treatment with abiraterone, apalutamide, or enzalutamide.

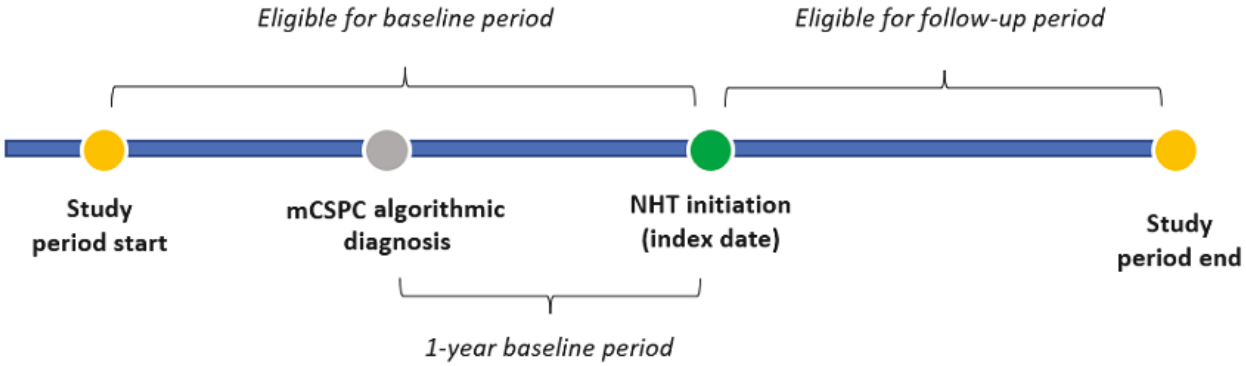
CCI [redacted]

8. RESEARCH METHODS

8.1. Study Design

This will be a non-interventional cohort study using existing administrative data from Original Medicare. Consistent with study objectives, the analytic goals will be to characterize treatment duration, time to next therapy, adherence, and next treatment received by drug in mCSPC patients initiating first-line NHT treatment. To account for the lack of mCSPC-specific ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification) codes, a modified version of a previously developed diagnostic algorithm for use in claims data will be implemented to identify the patient population of interest.[15] Patients with ≥8 weeks of continuous ADT use between 90 and 365 days prior to the index first-line NHT claim will be excluded from the analyses because they may be initiating treatment for mCRPC. Patients' index date will be assigned based on their first observed claim for relevant first-line NHTs during the index window (01 January 2020 to 31 December 2020 (or 1 year prior to end of data availability) and baseline covariates will be measured during the 365-day period prior to this date (Figure 1). The study exposure will be the NHT prescribed at index date (index NHT) stratified by the therapies of interest (abiraterone, enzalutamide, and apalutamide). Outcomes will be measured during a follow-up period of at least 6 months (or until death), defined as the time from the index date through the first of the following events: treatment switch, treatment discontinuation, death, or end of data availability. Study analyses will include fitting adjusted and unadjusted statistical models, with adjustment in the former based on relevant characteristics captured in the Medicare data as identified in the empirical literature.

Figure 1. Diagram of Study Period



8.2. Setting

Patients residing in the US will be identified and analyses conducted using claims and enrollment data covering the period from 01 January 2019 to end of data availability (at present 31 December 2021), with the identification window from 01 January 2020 to 31 December 2020 (or 1 year before the end of data availability). The start of the identification window was selected so that abiraterone, apalutamide, and enzalutamide were all approved for use in mCSPC. Claims data extending back to 1 January 2016 will be used to assess inclusion and exclusion criteria. The case definition for mCSPC will be based on the previously referenced diagnostic algorithm (see Inclusion Criteria and Exclusion Criteria below) with relevant adaptations applied where necessary to align with study scope.[15]

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study, with only inpatient hospitalization, outpatient facility, and carrier claims used to identify mCSPC patients:

Inclusion criteria:

1. Male patients with ≥1 claim (01 January 2020 to 31 December 2020 [or 1 year before the end of data availability]) for abiraterone, apalutamide, or enzalutamide (earliest is the index date) (Table 1).

   CCI [redacted]

2. ≥1 claim with a diagnosis code in any position for prostate cancer (ICD-10-CM: C61) prior to the index date

3. ≥1 claim with a diagnosis code for secondary metastasis on or after the initial prostate cancer diagnosis (ICD-10-CM codes C77 (excluding C77.5), C78, C79, C7B)

4. Index date within 30 days prior to or any time after the first claim for metastatic disease

5. ≥1 claim for ADT treatment in the 90 days prior to or within 30 days following the index date (Table 2)

6. ≥65 years old 12 months prior to the index date (baseline period)

7. Continuous enrollment in Medicare Parts A, B, and D throughout the baseline period

8. Continuous enrollment in Medicare Parts A, B, and D for ≥6 months following the index date (unless death) (follow-up period)

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. ≥1 claim with a diagnosis code for other cancers prior to or on the index date, excluding non-melanoma skin cancer at any time prior, and malignant neoplasm without specification of site and malignant neoplasm of the bone and articular cartilage between the date of metastatic disease and the index date.[14]

2. Claims indicating ≥8 weeks of continuous ADT use between 90 and 365 days prior to the index date or claims indicating 1st generation anti-androgen use between 90 and 365 days prior to the index date

3. Evidence of prostate cancer treatment including chemotherapy, NHT, PARP inhibitor, immunotherapy, radium-223, lutetium Lu 177 vipivotide tetraxetan, surgical castration (defined as ≥1 bilateral orchiectomy or ≥2 unilateral orchiectomies), or castration resistance diagnosis (ICD-10-CM code Z19.2) at any time prior to the index date (Table 2)

4. Evidence of prostate cancer treatment including chemotherapy, non-index NHT, 1st generation anti-androgen, PARP inhibitor, immunotherapy, radium-223, or lutetium Lu 177 vipivotide tetraxetan within 28 days on/after index date.

   CCI

5. ≥1 claim with a code indicating participation in a clinical trial on or after the index date (ICD-10-CM: Z00.6; Healthcare Common Procedure Coding System [HCPCS] modifiers: Q0, Q1)

6. Located outside the 50 states or Washington, DC during the baseline and follow-up periods

7. Enrollment in Medicare Advantage (Medicare Part C) during the baseline or follow-up periods

8.2.3. Inclusion/Exclusion Criteria Detailed Definitions

Table 1. NHTs Approved for mCSPC During Index Window

Novel hormonal therapy	National Drug Code (NDC)
Apalutamide	59676060012
Abiraterone	00093112589, 00143959721, 00378692078, 00378692191, 00904694804, 16714096301, 42291002412, 42292005701, 42292005703, 43598035804, 47335040181, 51407018112, 57894015012, 57894015512, 57894019506, 60505432701, 60687045511, 60687045521, 64679002101, 64980041812, 69238116507, 69238175406, 72205003092, 72606056601
Enzalutamide	00469012599, 00469062599, 00469072560

Table 2. Other Prostate Cancer Treatments

Hormonal therapy	NDC	HCPCS/Current Procedural Terminology [CPT]
ADT (LHRH agonists/antagonists)		
Goserelin	00310095036, 00310095130, 00310096036, 00310096130, 70720095036, 70720095130	J9202
Histrelin	54092063775, 55592050001, 67979000201, 67979050001	J1675, J9225, J9226, S0133, Q2020
Leuprolide	00024022205, 00024059707, 00024059722, 00024060545, 00024061030, 00024079375, 00026971101, 00074210803, 00074228203, 00074244003, 00074334603, 00074347303, 00074364103, 00074364203, 00074366303, 00074368303, 00074377903, 00074969403, 00182315499, 00185740014, 00185740085, 00300210601, 00300210801, 00300227001, 00300228201, 00300243701, 00300244001, 00300333601, 00300334301, 00300334601, 00300361224, 00300361228, 00300362624, 00300362628, 00300362901, 00300362906, 00300363901, 00300363906, 00300364101, 00300364201, 00300366301, 00300367301, 00300368301, 00703401418, 00703401419, 00703402419, 00781400332, 17314450001, 41616093640, 47335093640, 49884036826, 49884036845, 54569271300, 54569454700, 54569478500, 54569498200, 55390051505, 62935015350, 62935022104, 62935022205, 62935022305, 62935030230, 62935030330, 62935045245, 62935045345, 62935075275, 62935075375, 62935075474, 64523010001, 64523010002	C9430, J1950, J1951, J1952, J1954, J9217, J9218, J9219, Q0057
Triptorelin	00009521501, 00009521901, 00009766401, 00023590203, 00023590204, 00023590411, 00023590412, 00023590622, 00023590623, 24338015020, 52544009276, 52544015302, 52544015376, 52544015402, 52544015476,	C9016, J3315, J3316

Hormonal therapy	NDC	HCPCS/Current Procedural Terminology [CPT]
	52544018876, 52544018976, 74676590200, 74676590201, 74676590400, 74676590401, 74676590601	
Degarelix	55566830101, 55566830102, 55566830301, 55566840101, 55566840102, 55566840301	J9155
Relugolix	72974012001	
First Generation anti-androgens		
Bicalutamide	00093022001, 00093022056, 00310070510, 00310070530, 00310070539, 00378701705, 00378701793, 00781540901, 00781540931, 00781540964, 00904601946, 00904601960, 16714057101, 16714057102, 16714081601, 16714081602, 16729002301, 16729002310, 41616048583, 41616048588, 42291016830, 42291016850, 47335048583, 47335048588, 51079069201, 51079069203, 51991056001, 52152052602, 52152052630, 60429017701, 60429017705, 60429017730, 60505264201, 60505264203, 62559068030, 62559089030, 67253019103, 67253019110, 68084037411, 68084037421, 68084061211, 68084061221, 68382022401, 68382022405, 68382022406, 68382022410	
Flutamide	00085052503, 00085052505, 00085052506, 00093712005, 00093712086, 00172496058, 00172496070, 00185112505, 00185112518, 00185112588, 00555087004, 00555087063, 00591222718, 00591246618, 49884075305, 49884075313, 54868462800, 58016017000, 58016017030, 58016017060, 58016017090, 58016017099, 60429027218, 69097091591	2140244000
Nilutamide	00088111035, 00088111114, 24987011114, 59212011114, 62559017331, 66993021238	
Chemotherapy	**NDC**	**HCPCS**
Taxane Chemotherapy		
Cabazitaxel	00024582411	C9276, J9043
Docetaxel	00069914111, 00069914122, 00069914211, 00069914222, 00069914411, 00075800120, 00075800180, 00075800301, 00075800404, 00143920401, 00143920501, 00409020102, 00409020110, 00409020120, 00409020125, 00409020126, 00409020127, 00409036601, 00409036701, 00409036801, 00703572001, 00703573001, 00955102001, 00955102104, 00955102208, 16714046501, 16714050001, 16729012049, 16729022850, 16729023163, 16729023164, 16729023165, 16729026763, 16729026764, 16729026765, 25021022201, 25021022204, 25021022207, 25021024501,	J9170, J9171

Hormonal therapy	NDC	HCPCS/Current Procedural Terminology [CPT]
	25021024504, 39822212001, 39822218001, 39822220001, 42367012121, 42367012125, 42367012129, 43066000101, 43066000601, 43066001001, 43598025811, 43598025940, 43598038957, 43598061040, 43598061111, 45963073452, 45963073454, 45963073474, 45963076552, 45963079056, 47335028541, 47335028641, 47335032340, 47335089540, 47335093940, 50742046316, 63739093211, 63739097117, 66758005001, 66758005002, 66758005003, 66758095002, 66758095003, 66758095004, 67457053102, 67457053208, 67457053316, 67457078108, 72485021401, 72485021504, 72485021608	
Other Chemotherapy		
Carboplatin	00015321030, 00015321130, 00015321176, 00015321230, 00015321329, 00015321330, 00015321429, 00015321430, 00015321529, 00015321530, 00015321630, 00015323011, 00015323111, 00015323211, 00015323311, 00409112910, 00409112911, 00409112912, 00591221911, 00591222011, 00591333626, 00591333712, 00591333889, 00591345460, 00591368711, 00703324411, 00703324611, 00703324811, 00703324911, 00703326401, 00703326601, 00703326801, 00703326871, 00703327401, 00703327601, 00703327801, 00703423901, 00703423981, 00703424401, 00703424481, 00703424601, 00703424681, 00703424801, 00703424881, 00703424891, 10019091201, 10019091202, 10019091203, 10019091501, 10019091601, 10019091615, 10019091701, 10139006005, 10139006015, 10139006045, 10518010110, 10518010111, 10518010112, 15210006112, 15210006312, 15210006612, 15210006712, 16729029512, 16729029531, 16729029533, 16729029534, 25021020205, 25021020215, 25021020245, 25021020251, 47335015040, 47335015140, 47335028440, 47335030040, 47781060320, 47781060427, 47781060594, 47781060694, 50111096576, 50111096676, 50111096776, 50742044505, 50742044615, 50742044745, 50742044860, 55150033501, 55150038601, 55390015001, 55390015101, 55390015201, 55390015301, 55390015401, 55390015501, 55390015601, 55390022001, 55390022101, 55390022201, 61703033918, 61703033922, 61703033950, 61703033956, 61703033961, 61703033962, 61703033963, 61703036018, 61703036022, 61703036050, 63323016610,	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097

Hormonal therapy	NDC	HCPCS/Current Procedural Terminology [CPT]
	63323016720, 63323016721, 63323016800, 63323016905, 63323016915, 63323016945, 63323017205, 63323017215, 63323017245, 63323017260, 66758004701, 66758004702, 66758004703, 66758004704, 67457049154, 67457049215, 67457049346, 67457049461, 67457060820, 69448000512, 69448000531, 69448000533, 69448000534, 69448000538, 71288010005, 71288010015, 71288010045, 71288010051	
Cisplatin	00003307297, 00015307020, 00015307220, 00015322022, 00015322026, 00015322122, 00015322126, 00069008101, 00069008407, 00143950401, 00143950501, 00703574711, 00703574811, 10019091001, 10019091002, 16729028811, 16729028838, 44567050901, 44567051001, 44567051101, 44567053001, 47781060925, 47781061023, 49452207801, 49452207802, 49452207803, 55390009901, 55390011250, 55390011299, 55390018701, 55390041450, 55390041499, 63323010351, 63323010364, 63323010365, 67457042410, 67457042551, 68001028324, 68001028327, 68001028332, 68001028333, 70860020650, 70860020651	J9045
Oxaliplatin	00024059010, 00024059120, 00024059240, 00024059602, 00024059704, 00069006701, 00069007001, 00069007201, 00069007401, 00069101001, 00703398501, 00703398601, 00781331570, 00781331780, 00781931570, 00781931780, 00955102720, 00955172510, 00955172720, 00955173110, 00955173320, 16714072701, 16714072801, 16729033203, 16729033205, 25021021120, 25021021250, 25021023310, 25021023320, 41616017640, 41616017840, 43066001401, 43066001801, 45963061153, 45963061159, 45963063749, 45963063858, 47335004640, 47335004740, 47335017640, 47335017840, 47781059122, 47781059229, 51991021898, 51991021998, 51991092298, 51991092398, 55150033101, 55150033201, 60505613206, 60505613207, 60505613208, 61703036318, 61703036322, 61703036330, 61703036331, 61703036332, 61703036340, 63323017530, 63323017650, 63323021110, 63323021220, 63323065010, 63323065017, 63323065020, 63323065027, 63323075010, 63323075020, 66758005301, 66758005302, 67457044220, 67457046910, 67457047610, 68001034128, 68001034129, 68001034136, 68001034137, 68001046836, 68001046837, 70860020110, 70860020120,	J9263

Hormonal therapy	NDC	HCPCS/Current Procedural Terminology [CPT]
	71288010110, 71288010120, 72266012501, 72266012510, 72266012601, 72266012610, 72266016101, 72266016201, 72603010101, 72603030101	
Mitoxantrone	00205939336, 00205939372, 00703468001, 00703468091, 00703468501, 00703468591, 00703468601, 00703468691, 10518010510, 10518010511, 10518010512, 15210040335, 44087152001, 44087152501, 44087153001, 55390008301, 55390008401, 55390008501, 58406064003, 58406064005, 58406064007, 61703034318, 61703034365, 61703034366, 63323013210, 63323013212, 63323013215	J9293
Etoposide	00013733691, 00013734694, 00013735688, 00013736673, 00015306120, 00015306124, 00015306220, 00015306224, 00015308420, 00015309145, 00015309520, 00015309530, 00015309595, 00015340420, 00074148501, 00074148502, 00074148503, 00143937601, 00143951001, 00143951101, 00143951201, 00186157131, 00364302853, 00378326694, 00703564301, 00703564601, 00703565301, 00703565601, 00703565691, 00703565701, 00703565791, 00703565801, 00703566701, 00703566801, 10019093001, 10019093002, 16729011408, 16729011411, 16729011431, 16729026231, 51079096501, 51079096505, 53905029101, 55390029101, 55390029201, 55390029301, 55390049101, 55390049201, 55390049301, 58406071112, 58406071418, 61269041020, 63323010405, 63323010425, 63323010450, 68001026525, 68001026526, 68001026527	J8560, J9181
Immunotherapy	**NDC**	**HCPCS**
Pembrolizumab	00006302601, 00006302602, 00006302604, 00006302901, 00006302902	J9271, C9027
Sipuleucel-T	30237890006	Q2043, C9273
Radiotherapy	**NDC**	**HCPCS**
Radium-223	50419020801	A9606
Lutetium Lu 177 Vipivotide Tetraxetan	69488001061	A9607
PARP Inhibitors	**NDC**	**HCPCS**
Olaparib	00310065758, 00310066812, 00310066860, 00310067912, 00310067960	
Rucaparib	69660020191, 69660020291, 69660020391	
Talazoparib	00069029630, 00069119530	

Hormonal therapy	NDC	HCPCS/Current Procedural Terminology [CPT]
Niraparib	69656010330, 69656010390	
Surgical Castration	**ICD-10 Procedure Coding System (ICD-10-PCS)**	**CPT Codes**
Bilateral orchiectomy	0VTC4ZZ, 0VTC0ZZ	54520, 54522, 54530, 54535, 54690
Unilateral orchiectomy	0VT90ZZ, 0VT94ZZ, 0VTB0ZZ, 0VTB4ZZ	

8.3. Variables

Variables that will be included in this analysis are listed in Table 3, with additional detail regarding operational definitions provided where relevant. All variables will be constructed from the Medicare enrollment and claims data described in Section 8.4.

Table 3. Study Variables

Variable	Description
Exposure	
Index NHT compound	First NHT (abiraterone, enzalutamide, or apalutamide) used during the index window as defined by the presence of a claim containing one of the NDC codes listed in Table 1.
Follow-up Period Outcomes	
Treatment duration	Length of time (in days) that a patient uses NHT treatment. A patient will be considered "on treatment" from their initial claim date until the end of observation for any of the following reasons (earliest of dates below): • The end of data availability (at present December 31, 2021) • The patient's date of death • The day before a treatment switch • The day of treatment discontinuation (a 90-day gap in days supply will be considered as discontinuation) • Alternative definitions of discontinuation (ie, 30-day and 60-day gaps) will be explored in sensitivity analyses.
Discontinuation	An indicator for discontinuation of index treatment during the follow-up period, determined by the presence of a gap in treatment coverage of more than 90 days from the last day of medication availability (last observed claim + the days' supply for that claim).[16-18] The impact of varying this time period on study results will be explored via sensitivity analysis.
Treatment switch	Defined as the initiation of another prostate cancer treatment not given in conjunction with index treatment (Table 2 at any point following the index date.
Time to next therapy	Length of time (in days) from a patient's index date to first observed claim for another prostate cancer treatment (Table 2).
Adherence	The number of days supplied of an NHT over the total days of follow-up elapsed in a given period (eg, 3-month, 6-month, etc.) expressed as a percentage as the proportion of days covered (PDC), with the maximum value capped at 100% and overlapping prescriptions carried forward.[19]

Variable	Description
Follow up for overall survival	Length of time (in days) from a patient's index date to date of death or cutoff date for mortality data availability.
Overall survival	Length of time (in days) from a patient's index date to date of death. Patients who did not die will be censored as of the cutoff date for mortality data availability.
Demographic and socioeconomic characteristics	
Age	Age as of index date in years will be calculated based on the beneficiary's birth date and index date.
Age group	Age group will be a categorical variable for age defined as one of 65–74, 75–84, 85+.
Census region	Census region will be a categorical variable defined by categorizing the beneficiary's state of residence into Census regions (Northeast, South, Midwest, West) from the enrollment record covering the index date.
Index year	Index year will be defined as the year of the index date.
Race	Race will be a categorical variable for the beneficiary's self-reported race/ethnicity taking the categories Non-Hispanic White, Black or African-American, Asian/Pacific Islander, Hispanic, and Other (including other, American Indian/Alaska Native, and unknown race) from the enrollment record covering the index date.
Dual eligibility	Dual eligibility will be a binary indicator of whether a patient received dual-eligibility benefits for both Medicare and Medicaid.
Clinical characteristics	
Bone metastasis	Bone metastasis will be identified from inpatient, outpatient and Carrier claims with a diagnosis code for bone metastasis: ICD-10-CM: C79.51
Brain metastasis	Brain metastasis will be identified from inpatient, outpatient and Carrier claims with a diagnosis code for brain metastasis: ICD-10-CM: C79.31
Visceral metastasis	Visceral metastasis (including liver, lung, adrenal, peritoneal, and brain metastases) will be identified from inpatient, outpatient and Carrier claims with a diagnosis code for visceral metastasis: ICD-10-CM: C78.0x, C78.6x, C78.7x, C79.31, C79.7x
Baseline comorbidity score	Baseline comorbidity score will be a continuous Charlson Comorbidity Index based on research by.[20] The conditions in this index and their score weights are: - Myocardial infarction (1), - Congestive heart failure (1), - Peripheral vascular disease (1), - Cerebrovascular disease (1), - Chronic obstructive pulmonary disease (1), - Dementia (1), - Hemiplegia or paraplegia (2), - Diabetes without chronic complication (1), - Diabetes with chronic complication (2), - Moderate or severe renal disease (2), - Mild liver disease (1), - Moderate or severe liver disease (3), - Peptic ulcer disease (1) - Rheumatic disease (1), - AIDS/HIV (6).
Long-term corticosteroid use	Binary indicator for having long-term corticosteroid use, including hydrocortisone, prednisone, prednisolone, and dexamethasone during the baseline period: 1) treatment duration of ≥90 days with a gap of no more than 30 days between consecutive pharmacy claims (ie, less than 30 days between the end of the days supply of one claim and the start of the next claim) or, 2) at least two corticosteroid procedure claims (per Part B data) with at least 90 days apart during the baseline period.
Evidence of de novo mCSPC	Binary indicator for whether the earliest claim with a secondary metastasis diagnosis (ICD-10-CM codes C77 (excluding C77.5), C78, C79, C7B) following the initial prostate cancer diagnosis (ICD-10-CM: C61) was within 3 months of the initial prostate cancer diagnosis.

Variable	Description
ADT claim within 90 days prior to index date	Binary indicator for the presence of an ADT claim in the 90 days prior to the index date.
Time from first prostate cancer diagnosis to metastasis	Length of time (in months) from a patient's initial prostate cancer diagnosis to first metastatic diagnosis.
Time from first metastatic diagnosis to index date	Length of time (in months) from a patient's first metastatic diagnosis to the index date.
Time from ADT initiation to index date	Length of time (in months) from a patient's first ADT claim to the index date. If the patient initiated ADT after the index date, the time will be 0.
Time from ADT claim within 90 days before or 30 days after index date to index date	Length of time (in months) from a patient's first ADT claim within 90 days before or 30 days after the index date to the index date. If the patient initiated ADT after the index date, the time will be 0. This variable is intended to capture potential delay in NHT start relative to ADT potentially due to coverage reasons.
Baseline healthcare resource use	
Any inpatient admission	Binary variable representing any record of an inpatient admission during the 365-day baseline period.
Any emergency department visit	Binary variable representing any record of an emergency department visit during the 365-day baseline period.
Number of unique days with an outpatient claim	Cumulative number of days where an outpatient claim was submitted during the baseline period.
Nursing home category	Nursing home category will be a categorical variable for nursing home residence status defined by categorizing a beneficiary's use of nursing home services during the baseline period as none, short-stay only, any long stay.
Total healthcare spending	Total healthcare spending will be calculated for the baseline period as the total amount paid by all parties (Medicare, other payers, patient out-of-pocket).

8.4. Data Sources

The study will use a 100% census of data from the United States federal Medicare program on beneficiaries aged 65+ consistently enrolled in Original (also known as traditional or fee-for-service) Medicare insurance coverage for hospital (Part A), physician (Part B) and pharmacy (Part D) claims. These data are made available by the US Centers for Medicare and Medicaid Services (CMS). As of July 2019, there were over 38 million beneficiaries in Original Medicare, of whom 28 million qualified for Medicare benefits based on their age and were enrolled in Parts A and B and over 25 million had prescription drug coverage through Part D.[14] Part D coverage started on 01 January 2006, and the study will focus on enrollment and claims data from 01 January 2019 through end of data availability (at present 31 December 2021) but will use claims back to 01 January 2016 to assess medical history (eg, first metastatic diagnosis).

The research-identifiable data files provide a comprehensive and longitudinal picture of health care use among individuals aged 65 years and older. The Medicare data contractor assigns a unique beneficiary identification number to everyone who receives Medicare coverage and uses that number to identify an individual's records in all Medicare data files. This number does not change during a beneficiary's lifetime and each number is used only once.

The enrollment file contains monthly information on beneficiaries' enrollment in each part of Medicare as well as demographic information, residential location (at the 5-digit ZIP Code level), and date of death (from Medicare administrative files).

Claims data are available for all medical services covered by the program and are organized into data files based on the nature and source of the claim. The Inpatient, Outpatient and Skilled Nursing Facility files include institutional claims from hospitals for inpatient and outpatient services and from nursing homes for short-stay "skilled" admissions. The Carrier file includes fee-for-service claims submitted by professional providers, including physicians, physician assistants, clinical social workers, nurse practitioners. (Claims for some organizational providers, such as free-standing facilities, are also found in the Carrier file. Examples include independent clinical laboratories, ambulance providers, free-standing ambulatory surgical centers and free-standing radiology centers). There are separate files for claims for durable medical equipment, home health visits and hospice care.

CMS receives death information from a number of sources. The main sources CMS uses to develop its death information are:

- Medicare claims data from the Medicare Common Working File (CWF)
- Online date of death edits submitted by family members
- Benefit information used to administer the Medicare program collected from the Railroad Retirement Board (RRB) and the Social Security Administration (SSA)

8.5. Study Size

A previous feasibility assessment using the available 100% Medicare claims data from January 2016 through December 2020 identified a sample of approximately 1,600 patients meeting the inclusion criteria. This number is expected to increase with the addition of Medicare data from 2021.

The impact of restricting the index window to the period when all 3 NHTs of interest were approved and available from 01 January 2020 to 31 December 2020 (or 1 year before end of data availability) on study results will be additionally assessed in additional sensitivity analyses.[21]

8.6. Data Management

Pursuant to requirements guiding participation in the CMS Virtual Research Data Center (VRDC) Innovator program, Medicus Economics staff will access the Medicare claims and enrollment data only through the VRDC. As such, Medicus staff will not directly possess any beneficiary-level CMS data, and the only data to be downloaded from the VRDC will be summary-level statistics.

All data manipulation and analysis will be conducted on the CMS VRDC environment remotely by Medicus staff. Data manipulation and analysis will be conducted using SAS software (SAS Institute, Cary, NC) and R Statistical Software (v4.2.2; R Core Team 2023).

8.7. Data Analysis

Primary

1. Describe treatment duration among patients initiating first-line treatment with NHT (abiraterone, apalutamide, or enzalutamide) for mCSPC

Exploratory

1. CCI [redacted]
2. Describe time to next therapy for patients initiating first-line treatment with NHT for mCSPC CCI [redacted]
3. Describe adherence for patients initiating first-line treatment with NHT for mCSPC CCI [redacted]
4. Describe baseline characteristics (including demographics, disease characteristics, prostate cancer history, comorbidities, and resource use) overall for patients initiating first-line treatment with NHT and compare them across treatment cohorts
5. Describe next treatment received among the overall cohort of patients initiating first-line treatment with NHT for mCSPC and separately for patients with first-line treatment with abiraterone, apalutamide, or enzalutamide

CCI [redacted]

Primary Objective

Objective 1

Study objective: Describe treatment duration among patients initiating first-line treatment with NHT (abiraterone, apalutamide, or enzalutamide) for mCSPC

The analytic dataset for this objective will be constructed at the beneficiary level and will include the exposure of index NHT (abiraterone, apalutamide, or enzalutamide) as well as outcomes measured from the index date through the first of the following events: treatment switch, treatment discontinuation, death, or end of follow up.

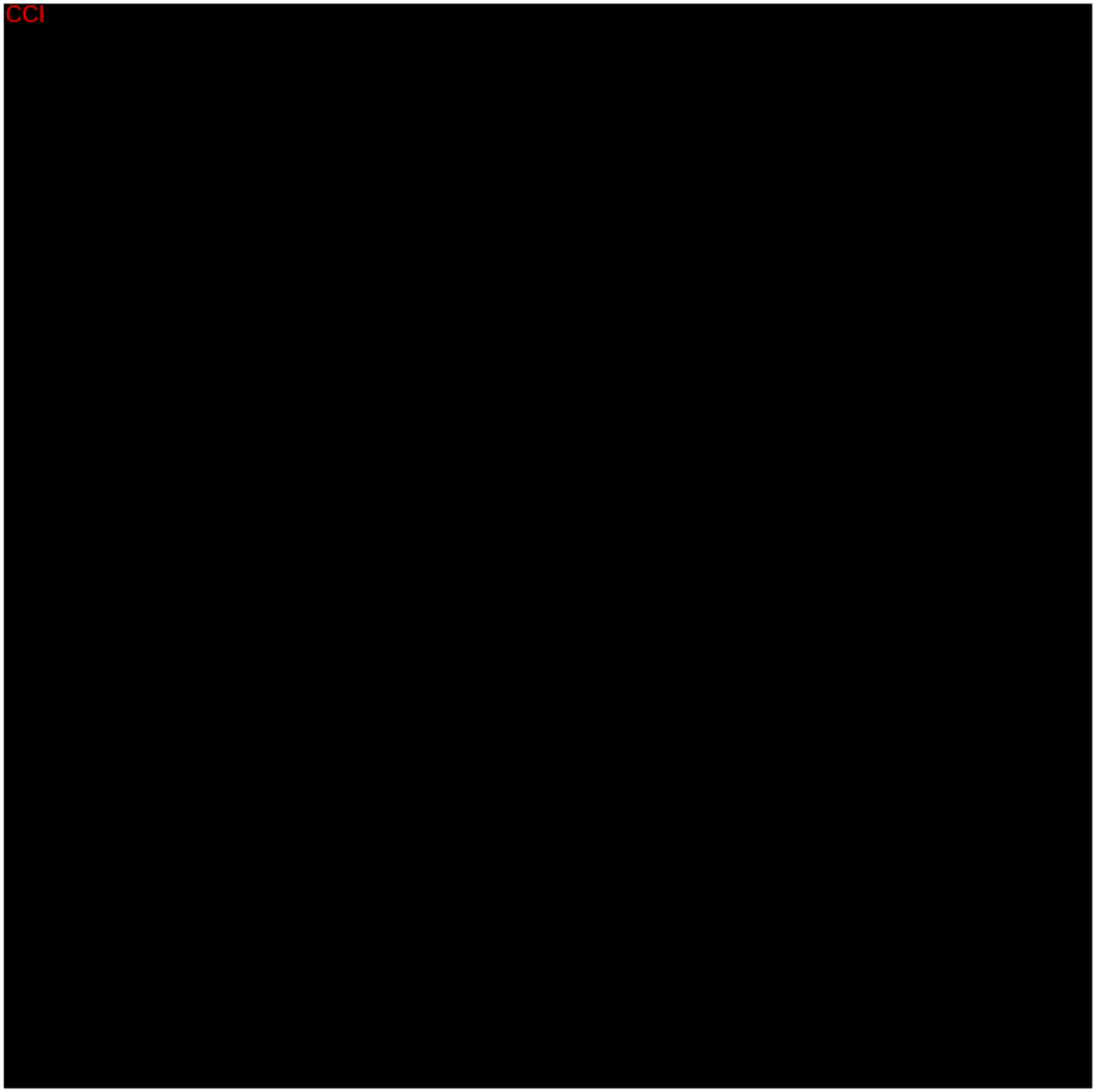
Analyses will include:

- Constructing frequency tables of reason for NHT treatment discontinuation/end of follow up disposition (discontinuation, death, treatment switch, end of index window) overall.

- Calculating descriptive statistics from Kaplan-Meier (KM) curves (eg, number of patients with event/censored, median, 95% Confidence Interval (CI), and interquartile range) for NHT treatment duration and constructing KM curve with end of the study period as a censoring event.

Exploratory Objectives

CCI



Exploratory Objective 2

Study objective: Describe time to next therapy for patients initiating first-line treatment with NHT for mCSPC [redacted]

The analytic dataset for this objective will be constructed at the beneficiary level and will include the exposure of index NHT compound as well as the time to next therapy outcome measured from the index date through the first of the following events: treatment switch, death, or end of follow up. [redacted]

Analyses will include:

- Calculating descriptive statistics from KM curves (eg, number of patients with event/censored, median, 95% CI, and interquartile range) for time to next therapy overall [redacted] and constructing KM curves [redacted]

[redacted]

Exploratory Objective 3

Study objective: Describe adherence for patients initiating first-line treatment with NHT for mCSPC [redacted]

The analytic dataset for this objective will be constructed at the beneficiary level and will include the exposure of index NHT (enzalutamide vs abiraterone and enzalutamide vs apalutamide) as well as outcomes measured from the index date through the first of the following events: treatment switch, treatment discontinuation, death, or end of follow up. [redacted]

Analyses will include:

- Calculating descriptive statistics (mean, standard deviation, median, and interquartile range) for adherence at three-month intervals over the first year following the index date overall [redacted]. Average adherence overall [redacted] at each 3-month interval in the follow-up period will be plotted to provide a visual representation of trends over time, with the understanding that the composition of patients at each time point will be changing due to switching, death, etc. The distribution of mean adherence in the year following the index date will additionally be examined to determine the magnitude of skew and kurtosis. The proportion of patients with adherence ≥80% will also be reported.

[redacted]

Exploratory Objective 4

Study objective: Describe baseline characteristics (including demographics, disease characteristics, prostate cancer history, comorbidities, and resource use) overall for patients initiating first-line treatment with NHT and compare them across treatment cohorts.

The analytic dataset for this objective will be constructed at the beneficiary level and include demographic, clinical, and resource use characteristics measured during the baseline period. Relevant summary measures are detailed below and will be generated for the overall patient sample and stratified by initial NHT therapy.

Analyses will include:

- Constructing frequency tables of treatment type by initial NHT compound.
- Calculating descriptive statistics (mean, standard deviation, median, and interquartile range for continuous measures; count and proportion for categorical measures) of all included characteristics at baseline (a) overall for patients initiating NHTs, and (b) by NHT type. Stratified descriptive statistics tables will include statistical tests (Analysis of variance [ANOVA] for means, nonparametric tests of equality of medians, and χ^2 tests for distributions of categorical variables) for each characteristic of the null hypothesis of joint equality across levels of the stratification variable.

Exploratory Objective 5

Study objective: Describe next treatment received among the overall cohort of patients initiating first-line treatment with NHT for mCSPC and separately for patients with first-line treatment with abiraterone, apalutamide, or enzalutamide.

The analytic dataset for this objective will be constructed at the beneficiary level and will include the exposure of index NHT as well as first subsequent mCSPC treatment identified using NDC codes from 1 and 2. Patients that die or reach the end of follow-up without initiating a subsequent mCSPC therapy will be separately characterized.

Analyses will include:

- Constructing frequency tables of next therapy type (eg, hormonal, chemo, other) overall and by initial NHT compound.
- Within initial NHT compound, more granular presentations of next therapy by compound will be provided and the distribution of next therapies by treatment type will be visualized via stacked bar charts.

CCI

[redacted]

CCI

[redacted]

8.8. Quality Control

The Medicare administrative data collection occurred in the past, and access to the data will be obtained from CMS. No additional insight into the data collection procedures is available beyond that which has been published by CMS. As a result, Medicus staff rely on quality control measures implemented by CMS during data collection.

Medicus has established protocols for quality control of analyses. All analyses are audited before the finalization of results. The auditor will independently review the conceptual and technical elements of the analysis and seek to identify any flaws or potential errors.

The auditor will understand the goal of the analysis and the expected results, and then review each step of the Medicus data analysis audit checklist (available upon request). The auditor will keep a list of questions or issues and then meet with the project lead to discuss any findings. If errors or issues are found that change the results, the auditor will perform an incremental audit to ensure that changes have been implemented properly and any change in results aligns with expectations about magnitude and direction.

8.9. Limitations of the Research Methods

There are several strengths to the study described here, which include:

- Use of the census of individuals enrolled in Original Medicare and diagnosed with mCSPC enhances generalizability to a very large portion of all mCSPC patients.

- Availability of data starting in 2005 to ensure ample opportunity to identify the occurrence of mCSPC and the ability to describe practice patterns through 2021 (at present).

- Medicare data offer access to measures not typically available in commercial and open-source claims databases, including beneficiary mortality and race/ethnicity.

There are also several limitations, which include:

- Possibly small sample sizes for some analyses, which would limit the statistical power to detect differences in outcomes across stratification levels.

- Limited generalizability of results outside of the Original Medicare population or to experience later than 2021 (at present).

- Relationships observed in statistical analyses may be an artifact of residual confounding due to an inability to capture certain factors in Medicare data, so results will be associational and not causal and subject to omitted variable bias.

- To prevent patient de-identification, outputs from CMS-provided data sources must be aggregated across at least 11 patients. Any outputs where N<11 must be redacted, and medians cannot be presented for any populations where N<50.

- Inaccuracy stemming from the intrinsic nature of administrative claims, including lack of clinical fidelity and lack of information on patients prior to their entry into the database.

- The impact of these limitations will be assessed to the extent possible via sensitivity analyses.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This continuation of research activity is covered by a review of the WCG Institutional Review Board (IRB). On 01 March 2021, the WCG IRB determined that this research activity (identified as WCG IRB work order #1-1409624-1), as conducted by Medicus Economics, was exempt from IRB review under 45 CFR § 46.104(d)(4), because, although the research involves the use of identifiable private information, (1) that information is recorded by the investigator in such a manner that the identity of the human subjects cannot readily by ascertained directly or through identifiers linked to the subjects, (2) the investigator will not contact the subjects, and (3) the investigator will not re-identify subjects.

At the same time, WCG IRB also approved a full waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization for use and disclosure of protected health information (PHI) based on adequate documentation that (1) the use or disclosure of the PHI involves no more than minimal risk to the individuals; (2) the research could not be practicably conducted without access to and use of the PHI; and (3) the research could not practicably be conducted without the waiver.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be considered for dissemination in the form of scientific publications (eg, an abstract/poster for presentation at a national conference, a manuscript for submission to a peer-reviewed journal).

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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