TREATMENT OF PROSTATE CANCER WITH A COMBINATION OF ABIRATERONE ACETATE AND NIRAPARIB

TECHNICAL FIELD OF THE INVENTION

The present disclosure relates to combinations of anti-cancer drugs, methods of treatment of prostate cancer with said combinations, and pharmaceutical formulations comprising said combinations.

BACKGROUND OF THE INVENTION

Prostate cancer is the most common non-cutaneous malignancy in men and the second leading cause of death in men from cancer in the western world.

Prostate cancer results from the uncontrolled growth of abnormal cells in the prostate gland. Once a prostate cancer tumor develops, androgens such as testosterone promote prostate cancer growth. At its early stages, localized prostate cancer is often curable with local therapy including, for example, surgical removal of the prostate gland and radiotherapy. However, when local therapy fails to cure prostate cancer, as it does in up to a third of men, the disease progresses into incurable metastatic disease (i.e., disease in which the cancer has spread from one part of the body to other parts).

Current therapeutic options for men with metastatic castration-resistant prostate cancer (mCRPC) that improve survival and limit progression include taxane-based chemotherapy, and androgen receptor-targeted agents such as apalutamide (ERLEADA®) and enzalutamide (XTANDI®).

Platinum-based chemotherapy has been tested in a number of clinical studies in molecularly unselected prostate cancer patients with limited results and significant toxicities.

More recently, abiraterone acetate (ZYTIGA®) plus prednisone has been approved for treating metastatic castrate resistant prostate cancer.

Niraparib is an orally available, highly selective poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases. Jones P, Wilcoxen K, Rowley M, Toniatti C. Niraparib: A Poly(ADP-ribose) Polymerase (PARP) Inhibitor for the Treatment of Tumors with Defective Homologous Recombination. J Med Chem. 2015 Apr 23;58(8):3302-3314.

PARPs are enzymes responsible for repair of DNA single-strand breaks (SSBs) through a process called base excision repair. PARP inhibition leads to an accumulation of unrepaired SSBs, which result in stalling and collapse of replication forks and, consequently, to double-stranded breaks (DSBs). Normally, DSBs are repaired through homologous recombination

(HR). If not repaired, DSBs result in cell death. When tumor cells with DNA-repair defects involving the HR pathway (e.g., Breast Cancer genes [BRCA]-l/2) are treated with a PARP inhibitor, they are unable to efficiently and accurately repair DSBs, which creates a synthetic lethal condition. In men with metastatic castration-resistant prostate cancers (mCRPC), tumors with DNA-repair anomalies account for approximately 20% to 30% of the sporadic cancers.

There is a need for therapeutic options for prostate cancer patients who either do not respond initially or become refractory to the existing treatments. Importantly, there is an unmet need for therapeutic options for prostate cancer patients.

SUMMARY OF THE INVENTION

The present disclosure relates to a combination of abiraterone acetate and niraparib, which can be administered to a mammal, in particular a human, suffering from an androgen receptor (AR)-related disease or condition, in particular cancer, more in particular prostate cancer.

These pharmaceutical formulations are fixed dose combinations of abiraterone acetate and niraparib.

An objective of the present invention is to provide therapies against prostate cancer, including, among others, hormone-sensitive prostate cancer, hormone-naïve high-risk prostate cancer, castration-resistant prostate cancer, metastatic castration resistant prostate cancer (mCRPC), metastatic castration sensitive prostate cancer (mCSPC), non-metastatic castration resistant prostate cancer (nmCRPC), biochemical recurrent (BCR) prostate cancer, and localized prostate cancer (LPC).

An objective of the present invention is to provide free-dose combinations (FrDC) of abiraterone acetate and niraparib tosylate monohydrate; or fixed-dose combinations (FDC) comprising abiraterone acetate and niraparib tosylate monohydrate.

An objective of the present invention is to provide pharmaceutical formulations that support patient compliance, therapy adherence, and therapy efficiency.

An objective of the present invention is to provide pharmaceutical formulations that reduce the tablet burden of the patients, e.g., from six or four tablets of abiraterone acetate and niraparib tosylate monohydrate per day to three, or preferably two or one tablet(s) per day.

An objective of the present invention is to provide fixed-dose combination (FDC) pharmaceutical formulations with comparable or improved stability or shelf life to the drug dosage forms formulated separately.

An objective of the present invention is to provide fixed-dose combination pharmaceutical formulations which are bioequivalent to the drug dosage forms when administered in separate dosage forms.

An objective of the present invention is to provide fixed-dose combination pharmaceutical formulations with an immediate release profile for both abiraterone acetate and niraparib.

An objective of the present invention is to provide fixed-dose combination pharmaceutical formulations with a good content uniformity or homogeneous distribution of abiraterone acetate and niraparib tosylate monohydrate. In some aspects, the abiraterone acetate and niraparib tosylate monohydrate are homogeneously distributed within an intragranular phase. In some aspects, the abiraterone acetate and niraparib tosylate monohydrate are homogenously distributed within the dosage form, e.g., tablet. In some aspects, where abiraterone acetate and niraparib tosylate monohydrate are prepared in separate granules, the respective granules are homogenously distributed in a granule blend. Abiraterone acetate and niraparib tosylate monohydrate drug substances have different particles sizes (d_{50} of 4-5 µm and d_{50} around 50 µm, respectively), different bulk densities, and different contents (33% and 5-10% (w/w), respectively) in the fixed-dose combinations of the present invention. When blending these two drug substances as such, they are prone to segregation, which causes problems with homogeneity in the blend and therefore dosage control in individual tablets. Administering an FDC with accurate and consistent amounts of the two drug substances is critical for ensuring safety and efficacy.

Content uniformity may be impacted by formulation manufacturing conditions, such as the inlet air temperature, spray rate, inlet air flow during granulation, and loss on drying during granulation.

An objective of the present invention is to provide granules comprising abiraterone acetate and niraparib tosylate monohydrate with a good stratified content uniformity.

An objective of the present invention is to provide granules comprising abiraterone acetate and niraparib tosylate monohydrate with a desired particle size distribution, that may be expressed in values of d_{10}, d_{50}, and/or d_{90}. If the granules are too small, this could result in issues during compression when preparing tablets. If the granules are too large, this could result in differences in content uniformity and undesired segregation, issues with compression during tableting, and issues with the dissolution and bioavailability of the APIs.

An objective of the present invention is to provide an immediate release film-coated fixed-dose combination pharmaceutical formulation for oral administration, whose ingredients do not cause oxidative degradation of abiraterone acetate, an API known to be sensitive to such degradation. The presence of organic or inorganic impurities and/or degradants and/or metabolites if out of trend can have an impact on patient safety or efficacy of the therapy.

An objective of the present invention is to provide fixed-dose combination pharmaceutical formulations with comparable dissolution profiles for abiraterone acetate and niraparib tosylate monohydrate relative to each other. Such a dissolution profile can support use of a fixed-dose

combination because both agents would be suitable for administration on the same schedule. Another objective of the present invention is to provide fixed-dose combination formulations with comparable or improved dissolution profiles for either one or both, and preferably both, active ingredients when compared to one or both of the respective drugs formulated separately, e.g., in their current commercially marketed formulations (such as abiraterone acetate tablets and niraparib tosylate monohydrate capsules). Dissolution profiles may be impacted by manufacturing conditions, such as the inlet air temperature, spray rate, inlet air flow during granulation, and by the tablet hardness.

An objective of the present invention is to provide fixed-dose combination pharmaceutical formulations with comparable or improved bioavailability for each drug when compared to the drugs dosed as separate formulations (e.g., in their currently marketed formulations, which are abiraterone acetate tablets and niraparib tosylate monohydrate capsules). Another objective of the present invention is to provide fixed-dose combination pharmaceutical formulations where the two active ingredients exhibit one or more comparable pharmacokinetic parameter relative to the separate formulations (e.g., similar or improved T_{max} and/or $t_{1/2}$, or % C_{max}). Reduced bioavailability relative to single agent dosing, or bioavailability parameters that do not support the same dosing schedule for both agents would lead to low plasma levels and impact efficacy of the therapy and could require increasing the frequency of dosing, number of doses, or both.

An objective of the present invention is to provide an immediate release film-coated fixed-dose combination pharmaceutical formulation for oral administration comprising 500 mg of abiraterone acetate and either 50 mg or 100 mg of free base niraparib, in tosylate monohydrate form.

An objective of the present invention is to provide an immediate release film-coated fixed-dose combination pharmaceutical formulation for oral administration comprising 375 mg of abiraterone acetate and either 50 mg or 100 mg of free base niraparib, in tosylate monohydrate form.

An objective of the present invention is to provide an immediate release film-coated fixed-dose combination pharmaceutical formulation for oral administration comprising 250 mg of abiraterone acetate and either 50 mg or 100 mg of free base niraparib, in tosylate monohydrate form.

An objective of the present invention is to provide fixed-dose combination pharmaceutical formulations with comparable or increased efficacy (e.g., due to increased bioavailability at the same doses) when compared to the drugs dosed separately.

In view of the divergent physicochemical properties of abiraterone acetate (lipophilic and poorly bioavailable) and niraparib tosylate monohydrate (hydrophilic and moderately to highly

bioavailable), it is also an objective of the present invention to provide a technical solution to formulators when compounding the two drugs together.

The present disclosure relates to a method for the treatment of prostate cancer in a male human patient comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus a glucocorticoid, e.g., prednisone, hydrocortisone, dexamethasone, prednisolone, including methylprednisolone.

The present disclosure relates to a method for the treatment of mCRPC in a male human patient with mCRPC, the method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone. In an aspect, the mCRPC treatment is first-line (L1) treatment of mCRPC. In an aspect, the patient has not been treated with abiraterone acetate plus prednisone for more than 5 months. In an aspect, the patient is positive for homologous recombination deficiency (HRD), or the patient is not positive for HRD. In an aspect, the HRD status is detected by monoallelic or biallelic alterations in one or more DNA repair genes, including without being limited to, BRCA1 (Breast Cancer gene 1), BRCA2 (Breast Cancer gene 2), ATM (ataxia-telangiectasia mutated), FANCA (Fanconi Anemia Complementation Group A gene), PALB2 (Partner and Localizer of BRCA2 gene), CHEK2 (Checkpoint Kinase 2 gene), BRIP1 (BRCA1 Interacting Protein C-terminal Helicase 1 gene), HDAC2 (Histone deacetylase 2), or CDK12 (Cyclin Dependent Kinase 12). In an aspect, the patient has received gonadotropin releasing hormone agonists (GnRHa) therapy or has undergone bilateral orchiectomy, prior to the treatment with the pharmaceutical formulation, plus prednisone. In an aspect, GnRHa therapy continues during the treatment with the pharmaceutical formulation, plus prednisone, if not surgically castrated.

The present disclosure relates to a method for the treatment of mCSPC in a male human patient with mCSPC, such patient having deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCSPC, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone. In an aspect, the deleterious germline or somatic HRR gene mutation is in one or more genes, including without being limited to, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B (RAD51 paralog B), and RAD54L (RAD54-Like). In an aspect, the patient has undergone ADT prior to the treatment with the pharmaceutical formulation, plus prednisone. In an aspect, said ADT is a medical or surgical castration. In an aspect, said ADT started within 6 months, preferably at least 14 days, prior to the treatment with the pharmaceutical formulation, plus prednisone. In an aspect, the patient undergoes ADT during the treatment with the pharmaceutical formulation, plus prednisone. In an aspect, the patient has not undergone prior therapy with a next generation

androgen signaling inhibitor therapy (e.g., abiraterone acetate, enzalutamide, apalutamide, darolutamide, nilutamide, flutamide, bicalutamide, and the like). In an aspect, the patient has received docetaxel or cabazitaxel prior to the treatment with the pharmaceutical formulation, plus prednisone. In an aspect, the patient has received radiation or surgical intervention, prior to the treatment with the pharmaceutical formulation, plus prednisone. In an aspect, the patient has received abiraterone acetate plus prednisone, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has received abiraterone acetate plus prednisone, during a month prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has received treatments for localized prostate cancer, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said treatments for localized prostate cancer have been completed at least 1 year prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said treatments for localized prostate cancer are up to 3 years of ADT including radiation therapy, prostatectomy, lymph node dissection, or systemic therapies.

The present disclosure relates to a method for the treatment of mCRPC in a male human patient with mCRPC, with or without DNA-repair gene defects (DRD) or HRD, and optionally with cyclin dependent kinase 12 (CDK12) pathogenic alterations, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone. In an aspect, the patient continues with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated. In an aspect, the patient has been exposed to anti-androgens selected from nilutamide, flutamide, bicalutamide, enzalutamide, apalutamide, darolutamide, and abiraterone acetate; prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said anti-androgens are washed-out prior to the treatment with the pharmaceutical formulation plus prednisone.

The present disclosure relates to a method for the treatment of high risk and/or lymph node positive prostate cancer in a male human patient with high risk and/or lymph node positive prostate cancer, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone and leuprorelin acetate, prior to, during, and after radiotherapy. In an aspect, said radiotherapy is stereotactic body radiotherapy (SBRT) or ultra-hypofractionated radiotherapy, with a total dose of about 37.5 to 40 grays (Gy).

The present disclosure relates to a method for the treatment of castration-naïve prostate cancer in a male human patient with castration-naïve prostate cancer, with or without metastases, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described

herein, plus prednisone. In an aspect, the patient continues with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated.

The present disclosure relates to a method for the treatment of biochemical recurrent prostate cancer in a male human patient with biochemical recurrent prostate cancer, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone. In an aspect, said biochemical recurrent prostate cancer is detected by: i) a prostate-specific antigen (PSA) rise of $\geq$ 2.0 ng/mL above the nadir; or ii) next generation imaging (NGI) including prostate-specific membrane antigen positron emission tomography (PSMA-PET). In an aspect, the patient is HRD biomarker positive, high risk, and/or with oligometastatic disease. In an aspect, the HRD biomarker positive is one or more of, without being limited to, BRCA1, BRCA2, ATM, BRIP1, CDK12, CDK17, CHEK2, FANCA, HDAC2, PALB2, PPP2R2A, RAD51B, and RAD54L.

The present disclosure relates to a method for the treatment of locally advanced prostate cancer in a male human patient with locally advanced prostate cancer and who is a candidate for primary radiotherapy, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone.

The present disclosure relates to a method for the treatment of mCRPC in a male human patient with mCRPC optionally having received prior chemotherapy comprising docetaxel or cabazitaxel, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone.

The present disclosure relates to a method for the treatment nmCRPC in a male human patient with nmCRPC, said method comprising administering to the patient an effective amount of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate as described herein, plus prednisone. In an aspect, the patient has a PSA doubling time equal to or less than 10 months and is HRD positive. In an aspect, the patient is HRD positive. In an aspect, the patient has high-risk BCR.

In the methods of treatment disclosed herein, said pharmaceutical formulation may be a free-dose combination (FrDC) of abiraterone acetate and niraparib tosylate monohydrate; or a fixed-dose combination (FDC) comprising abiraterone acetate and niraparib tosylate monohydrate. In an aspect, the FrDC or FDC comprise, each independently, about 50 mg eq. niraparib and about 500 mg abiraterone acetate; about 100 mg eq. niraparib and about 500 mg abiraterone acetate; about 50 mg eq. niraparib and about 375 mg abiraterone acetate; about 100 mg eq. niraparib and about 375 mg abiraterone acetate; about 50 mg eq. niraparib and about 250 mg

abiraterone acetate; about 100 mg eq. niraparib and about 250 mg abiraterone acetate; about 33 mg eq. niraparib and about 333 mg abiraterone acetate; or about 67 mg eq. niraparib and about 333 mg abiraterone acetate. In an aspect, the FrDC or FDC are oral dosage forms. In an aspect, the oral dosage form is a tablet, a capsule, or a sachet.

In the methods of treatment disclosed herein, the fixed-dose combination (FDC) comprising abiraterone acetate and niraparib, preferably niraparib tosylate monohydrate, is as defined throughout the present disclosure.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use with prednisone, in treating prostate cancer in a patient, such as mCRPC, such as first-line (L1) mCRPC. In as aspect, the patient has not been treated with abiraterone acetate and prednisone for more than 5 months. In an aspect, the patient is positive for homologous recombination deficiency (HRD), or the patient is not positive for HRD. In an aspect, the HRD status is detected by monoallelic or biallelic alterations in one or more DNA repair genes, including without being limited to, BRCA1 (Breast Cancer gene 1), BRCA2 (Breast Cancer gene 2), ATM (ataxia-telangiectasia mutated), FANCA (Fanconi Anemia Complementation Group A gene), PALB2 (Partner and Localizer of BRCA2 gene), CHEK2 (Checkpoint Kinase 2 gene), BRIP1 (BRCA1 Interacting Protein C-terminal Helicase 1 gene), HDAC2 (Histone deacetylase 2), or CDK12 (Cyclin Dependent Kinase 12). In an aspect, the patient has received gonadotropin releasing hormone agonists (GnRHa) therapy or has undergone bilateral orchiectomy, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the GnRHa therapy continues during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use with prednisone, in treating mCSPC in patients having deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCSPC. In an aspect, the deleterious germline or somatic HRR gene mutation is in one or more genes, including without being limited to, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, and RAD54L. In an aspect, the patient has undergone ADT prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said ADT is medical or surgical castration. In an aspect, said ADT started within 6 months, preferably at least 14 days, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient undergoes ADT during the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has not undergone prior therapy with a next generation androgen signaling inhibitor therapy (e.g., abiraterone acetate, enzalutamide, apalutamide, darolutamide, nilutamide, flutamide, bicalutamide, and the like). In an aspect, the patient has received

docetaxel or cabazitaxel prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has received radiation or surgical intervention, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has received abiraterone acetate plus prednisone, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has received abiraterone acetate plus prednisone, during a month prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, the patient has received treatments for localized prostate cancer, prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said treatments for localized prostate cancer have been completed at least 1 year prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said treatments for localized prostate cancer are up to 3 years of ADT including radiation therapy, prostatectomy, lymph node dissection, or systemic therapies.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use plus prednisone, in treating mCRPC in patients with mCRPC, with or without DNA-repair gene defects (DRD) or HRD, and optionally with cyclin dependent kinase 12 (CDK12) pathogenic alterations. In an aspect, the patient continues with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated. In an aspect, the patient has been exposed to anti-androgens selected from nilutamide, flutamide, bicalutamide, enzalutamide, apalutamide, darolutamide, and abiraterone acetate; prior to the treatment with the pharmaceutical formulation plus prednisone. In an aspect, said anti-androgens are washed-out prior to the treatment with the pharmaceutical formulation plus prednisone.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use plus prednisone and leuprorelin acetate, in treating high risk and/or lymph node positive prostate cancer in patients having high risk and lymph node positive prostate cancer, prior to, during, and after radiotherapy. In an aspect, said radiotherapy is stereotactic body radiotherapy (SBRT) or ultra-hypofractionated radiotherapy, with a total dose of about 37.5 to 40 Gy.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use plus prednisone, in treating castration-naïve prostate cancer in patients having castration-naïve prostate cancer, with or without metastases. In an aspect, GnRHa therapy continues during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use plus prednisone, in treating biochemical recurrent prostate cancer in patients having biochemical recurrent prostate cancer. In an aspect, said biochemical recurrent prostate cancer is detected by: i) a prostate-specific antigen (PSA) rise of $\geq$ 2.0 ng/mL above the nadir; or ii) next generation imaging (NGI) including prostate-specific membrane antigen positron emission tomography (PSMA-PET). In an aspect, the patients are HRD biomarker positive, high risk, and/or with oligometastatic disease. In an aspect, the HRD biomarker positive is one or more of, without being limited to, BRCA1, BRCA2, ATM, BRIP1, CDK12, CDK17, CHEK2, FANCA, HDAC2, PALB2, PPP2R2A, RAD51B, and RAD54L.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use plus prednisone, in treating locally advanced prostate cancer in patients having locally advanced prostate cancer and who are candidates for primary radiotherapy.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use, plus prednisone, in treating mCRPC in patients having mCRPC optionally having received prior chemotherapy comprising docetaxel or cabazitaxel.

The present disclosure relates to a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate, as a combined preparation for simultaneous, separate or sequential use, plus prednisone, in treating nmCRPC in patients having nmCRPC. In an aspect, the patients have a PSA doubling time equal to or less than 10 months and are HRD positive. In an aspect, the patients are HRD positive. In an aspect, the patients have high-risk BCR.

The pharmaceutical formulation for the uses disclosed herein may be a free-dose combination (FrDC) of abiraterone acetate and niraparib; or a fixed-dose combination (FDC) comprising abiraterone acetate and niraparib. The pharmaceutical formulation for the uses disclosed herein may be a FrDC of abiraterone acetate and niraparib tosylate monohydrate; or a FDC comprising abiraterone acetate and niraparib tosylate monohydrate. In an aspect, the FrDC or FDC comprise, each independently, about 50 mg niraparib eq. (equivalent to niraparib free base) and about 500 mg abiraterone acetate; about 100 mg niraparib eq. and about 500 mg abiraterone acetate; about 50 mg niraparib eq. and about 375 mg abiraterone acetate; about 100 mg niraparib eq. and about 375 mg abiraterone acetate; about 50 mg niraparib eq. and about 250 mg abiraterone acetate; about 100 mg niraparib eq. and about 250 mg abiraterone acetate; about 33 mg niraparib eq. and about 333 mg abiraterone acetate; or about 67 mg niraparib eq. and about 333 mg abiraterone acetate. In an aspect, the FrDC or FDC are oral dosage forms. In an aspect, the oral dosage form is a tablet, a capsule, or a sachet.

The fixed-dose combination (FDC) comprising abiraterone acetate and niraparib tosylate monohydrate (or niraparib) is as defined throughout the present disclosure.

The present disclosure relates to a granule composition comprising abiraterone acetate, niraparib, and a pharmaceutically acceptable carrier. The present disclosure relates to a pharmaceutical formulation, such as an oral dosage form, comprising the granule composition.

In an aspect, the granules consist essentially of abiraterone acetate, niraparib, and a pharmaceutically acceptable carrier. In an aspect, said granules have a particle size distribution with a d_{50} of about 200 to about 500 μm, or of about 231 to about 396 μm; with a d_{10} of about 50 to about 250 μm, or of about 93 to about 192 μm; and/or with a d_{90} of about 500 to about 900 μm, or of about 616 to about 723 μm.

In an aspect, a first portion of the granules consists essentially of abiraterone acetate and a pharmaceutically acceptable carrier; and a second portion of the granules consists essentially of niraparib and a pharmaceutically acceptable carrier.

In an aspect, the niraparib is in the salt form of tosylate monohydrate, sulfate, benzenesulfate, fumarate, succinate, camphorate, mandelate, camsylate, lauryl sulfate, or a mixture of tosylate monohydrate and lauryl sulfate. In an aspect, the niraparib tosylate monohydrate is in crystal form. In an aspect, the abiraterone acetate is in crystal form. In an aspect, the present disclosure relates to a pharmaceutical formulation comprising niraparib lauryl sulfate and a pharmaceutically acceptable carrier. In an aspect, the present disclosure relates to a pharmaceutical formulation comprising a mixture of niraparib tosylate monohydrate and niraparib lauryl sulfate, and a pharmaceutically acceptable carrier.

In an aspect, the pharmaceutically acceptable carrier of the granule composition comprises a wetting agent, a diluent, a disintegrant, optionally a glidant, optionally a lubricant, and optionally a binder. In an aspect, the diluent is lactose, and said lactose is also used as a binder. In an aspect, the disintegrant is crospovidone.

The present disclosure further relates to a pharmaceutical formulation, e.g., an oral dosage form, comprising the granule composition described herein. In an aspect, the formulation or oral dosage form comprises about 50 mg niraparib eq. and about 500 mg abiraterone acetate; about 100 mg niraparib eq. and about 500 mg abiraterone acetate; about 50 mg niraparib eq. and about 375 mg abiraterone acetate; about 100 mg niraparib eq. and about 375 mg abiraterone acetate; about 50 mg niraparib eq. and about 250 mg abiraterone acetate; about 100 mg niraparib eq. and about 250 mg abiraterone acetate; about 33 mg niraparib eq. and about 333 mg abiraterone acetate; or about 67 mg niraparib eq. and about 333 mg abiraterone acetate.

In an aspect, the oral dosage form is a tablet, wherein the pharmaceutically acceptable carrier comprises a wetting agent, a diluent, a disintegrant, a glidant, a lubricant, optionally a binder,

and optionally a coating material. In an aspect, the wetting agent is sodium lauryl sulfate (SLS) and is present in the dosage form in a percentage from about 3 to 6 % (w/w). In an aspect, the wetting agent is SLS and is present in the final dosage forms in a by weight ratio versus abiraterone acetate of about 0.05:1 to 0.2:1 (SLS:abiraterone acetate), preferably about 0.1:1, more preferably about 0.11:1, about 0.12:1, or about 0.123:1. In an aspect, the SLS is present both in the intragranular and extragranular phases of the tablet. In an aspect, the disintegrant is crospovidone and is present both in the intragranular and extragranular phases of the tablet. In as aspect, the diluent of the extragranular phase is silicified microcrystalline cellulose. In an aspect, the tablet has a hardness of 250 to 350 N. In an aspect, the tablet has a stratified content uniformity from 75% to 125%, or from 90% to 110%. In an aspect, the tablet has a blend uniformity with a relative standard deviation up to 3%.

In an aspect, the tablet comprises about 500 mg of abiraterone acetate and about 50 mg of niraparib eq.; and wherein (i) greater than 40%, or about 50%, of abiraterone acetate dissolves after 5 minutes, (ii) greater than 75%, or about 80 or 81%, of abiraterone acetate dissolves after 10 minutes, (iii) greater than 85%, or about 89 or 90% of abiraterone acetate dissolves after 15 minutes, (iv) greater than 87%, or about 92%, of abiraterone acetate dissolves after 20 minutes; (v) greater than 90%, or about 95%, of abiraterone acetate dissolves after 30 minutes, (vi) greater than 91%, or about 96%, of abiraterone acetate dissolves after 45 minutes, (vii) greater than 92%, or about 97%, of abiraterone acetate dissolves after 60 minutes, (viii) greater than 93%, or about 98%, of abiraterone acetate dissolves after 90 minutes, or (ix) greater than 93%, or about 98%, of abiraterone acetate dissolves after 120 minutes; when measured by the USP Paddle method at 75 rpm in 900 mL of an aqueous solution comprising 0.05 mM sodium phosphate buffer with 0.25% (w/v) sodium lauryl sulfate at pH 4.5 and a temperature of 37.0 ± 0.5 °C.

In an aspect, the tablet comprises about 500 mg of abiraterone acetate and about 100 mg of niraparib eq.; and wherein (i) greater than 36%, or about 41%, of abiraterone acetate dissolves after 5 minutes, (ii) greater than 67%, or about 72%, of abiraterone acetate dissolves after 10 minutes, (iii) greater than 76%, or about 81%, of abiraterone acetate dissolves after 15 minutes, (iv) greater than 81%, or about 86%, of abiraterone acetate dissolves after 20 minutes, (v) greater than 85 or 86%, or about 90 or 91%, of abiraterone acetate dissolves after 30 minutes, (vi) greater than 90%, or about 95%, of abiraterone acetate dissolves after 45 minutes, (vii) greater than 90 or 91%, or about 95 or 96%, of abiraterone acetate dissolves after 60 minutes, (viii) greater than 93%, or about 98%, of abiraterone acetate dissolves after 90 minutes, or (ix) greater than 94%, or about 99%, of abiraterone acetate dissolves after 120 minutes; when measured by the USP Paddle method at 75 rpm in 900 mL of an aqueous solution comprising 0.05 mM sodium phosphate buffer with 0.25% (w/v) sodium lauryl sulfate at pH 4.5 and a temperature of 37.0 ± 0.5 °C.

In an aspect, the tablet comprises about 500 mg of abiraterone acetate and about 50 mg of niraparib eq.; and wherein (i) greater than 30 or 35%, or about 39 or 40%, of niraparib dissolves after 5 minutes, (ii) greater than 79 or 80%, or about 84 or 85%, of niraparib dissolves after 10 minutes, (iii) greater than 90%, or about 95%, of niraparib dissolves after 15 minutes, (iv) greater than 92%, or about 97%, of niraparib dissolves after 20 minutes, (v) greater than 93%, or about 98%, of niraparib dissolves after 30 minutes, (vi) greater than 93%, or about 98%, of niraparib dissolves after 45 minutes, (vii) greater than 93%, or about 98%, of niraparib dissolves after 60 minutes, (viii) greater than 93%, or about 98%, of niraparib dissolves after 90 minutes, or (ix) greater than 93%, or about 98%, of niraparib dissolves after 120 minutes; when measured by the USP Paddle method at 75 rpm in 900 mL of an aqueous solution comprising 0.05 mM sodium phosphate buffer with 0.25% (w/v) sodium lauryl sulfate at pH 4.5 and a temperature of 37.0 ± 0.5 °C.

In an aspect, the tablet comprises about 500 mg of abiraterone acetate and about 100 mg of niraparib eq.; and wherein (i) greater than 23%, or about 28%, of niraparib dissolves after 5 minutes, (ii) greater than 64%, or about 69%, of niraparib dissolves after 10 minutes, (iii) greater than 80 or 81%, or about 85 or 86%, of niraparib dissolves after 15 minutes, (iv) greater than 87%, or about 92%, of niraparib dissolves after 20 minutes, (v) greater than 90%, or about 95%, of niraparib dissolves after 30 minutes, (vi) greater than 91%, or about 96%, of niraparib dissolves after 45 minutes, (vii) greater than 92%, or about 97%, of niraparib dissolves after 60 minutes, (viii) greater than 92%, or about 97%, of niraparib dissolves after 90 minutes, or (ix) greater than 92%, or about 97%, of niraparib dissolves after 120 minutes; when measured by the USP Paddle method at 75 rpm in 900 mL of an aqueous solution comprising 0.05 mM sodium phosphate buffer with 0.25% (w/v) sodium lauryl sulfate at pH 4.5 and a temperature of 37.0 ± 0.5 °C.

In an aspect, the tablet dosage forms are bioequivalent, when administered orally on an equivalent dose basis, to free-dose combinations of abiraterone acetate and niraparib (e.g., wherein one or more pharmacokinetic parameters are within 20% or within 10% or within 5% of the respective values after dosing with free-dose combinations or single agents).

In an aspect, the oral dosage form is a capsule or a sachet, optionally further comprising a diluent.

In an aspect, the oral dosage form is a fixed-dose combination (FDC).

The present disclosure also relates to the pharmaceutical formulation or oral dosage form described herein, for use in the treatment of prostate cancer in a patient. Similarly, the present disclosure also relates to a method of treatment of prostate cancer in a patient, said method comprising administering to the patient said pharmaceutical formulation or oral dosage form.

In an aspect, the prostate cancer is metastatic prostate cancer, advanced prostate cancer, regional prostate cancer, locally advanced prostate cancer, localized prostate cancer, non-metastatic prostate cancer, non-metastatic advanced prostate cancer, non-metastatic regional prostate cancer, non-metastatic locally advanced prostate cancer, non-metastatic localized prostate cancer, hormone-naïve prostate cancer, chemotherapy-naïve prostate cancer, castration-naïve cancer with or without metastases, radiation-naïve prostate cancer, castration-resistant prostate cancer (CRPC), non-metastatic CRPC (nmCRPC), localized CRPC, locally advanced CRPC, regional CRPC, advanced CRPC, metastatic CRPC (mCRPC), mCRPC in patients having biallelic DNA-repair gene defect (DRD) or HRD; mCRPC in patients having monoallelic DRD or HRD; mCRPC in patients having no DRD or HRD; mCRPC in patients having DRD or HRD and having received taxane and/or androgen receptor-targeted therapy, mCRPC in patients having received docetaxel or cabazitaxel; CRPC in patients having received hormone therapy (for example enzalutamide, darolutamide, apalutamide), CRPC in patients having received taxane therapy (for example docetaxel, mitoxantrone, cabazitaxel), chemotherapy-naïve CRPC, chemotherapy-naïve mCRPC, hormone-naïve CRPC, hormone-naïve mCRPC, CRPC with progression, CRPC with visceral metastases, CRPC with visceral metastases in patients having received hormone therapy (for example enzalutamide, darolutamide, apalutamide), CRPC with visceral metastases in patients having received taxane therapy (for example docetaxel, mitoxantrone, cabazitaxel), CRPC with visceral metastases and progression, castration-sensitive prostate cancer (CSPC), non-metastatic CSPC (nmCSPC), localized CSPC, locally advanced CSPC, regional CSPC, advanced CSPC, metastatic CSPC (mCSPC), chemotherapy-naïve CSPC, chemotherapy-naïve mCSPC, hormone-naïve CSPC, hormone-naïve mCSPC, hormone-sensitive prostate cancer (HSPC), hormone-dependent prostate cancer, androgen-dependent prostate cancer, androgen-sensitive prostate cancer, biochemically relapsed HSPC, metastatic HSPC (mHSPC), hormone-resistant prostate cancer (HRPC), non-metastatic HRPC (nmHRPC), localized HRPC, locally advanced HRPC, regional HRPC, advanced HRPC, metastatic HRPC (mHRPC), recurrent prostate cancer, prostate cancer with prostate specific antigen (PSA) persistence or recurrence after prostatectomy with or without distant metastases, radiation-resistant prostate cancer, and any combination thereof. In an aspect, the patient has first-line (L1) mCRPC and is positive for DRD or HRD. In an aspect, the patient has deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCSPC. In an aspect, the patient has mCRPC or CRPC with visceral metastases, with or without DNA-repair gene defects (DRD), and optionally with cyclin dependent kinase 12 (CDK12) pathogenic alterations. In an aspect, the patient has high-risk localized prostate cancer.

In an aspect, the patient is in a risk group selected from very low, low, intermediate favorable, intermediate unfavorable, high, very high, and regional. In an aspect, the medical use or method of treatment comprises administering about 666 to about 1500 mg/day of abiraterone acetate; administering about 999 to about 1500 mg/day of abiraterone acetate; administering about 666

mg/day of abiraterone acetate; or administering about 1000 mg/day of abiraterone acetate. In an aspect, the medical use or method of treatment comprises administering about 33 to about 300 mg/day of niraparib eq.; administering about 100 to about 200 mg/day of niraparib eq.; administering about 66 mg/day of niraparib eq.; administering about 100 mg/day of niraparib eq.; administering about 134 mg/day of niraparib eq.; or administering about 200 mg/day eq. of niraparib. In an aspect, the medical use or method of treatment comprises administering 1, 2, or 3 oral dosage forms per day. In an aspect, the medical use or method of treatment comprises administering the oral dosage form(s) once a day (q.d.) or two times a day (b.i.d.); preferably once a day at least 1 hour before a meal or at least two hours after a meal. In an aspect, the medical use or method of treatment comprises administering separately about 1 to about 60 mg/day of prednisone; about 5 to about 15 mg/day of prednisone; about 9 to about 11 mg/day of prednisone; about 10 mg/day of prednisone; about 5 mg/day of prednisone; or about 5 mg/day of prednisone.

The present disclosure also relates to a process for preparing certain of the granule compositions disclosed herein, comprising the steps of:

(a) preparing a binder solution comprising a wetting agent;

(b) blending the binder solution of step (a) with abiraterone acetate, niraparib, and a diluent, optionally in the presence of a disintegrant;

(c) wet granulating the blend obtained from step (b);

(d) drying the product obtained from step (c).

In an aspect, the binder solution comprises a binder, the wetting agent and a solvent. In an aspect, the inlet air temperature during the wet granulating of step (c), is from 25 °C to 65 °C. In an aspect, the spray rate during the wet granulating of step (c), is from 190 to 300 g/min. In an aspect, the inlet air flow during the wet granulating of step (c), is from 800 to 1300 m^3/h.

The present disclosure also relates to a process for preparing certain of the granule compositions disclosed herein, comprising the steps of:

(a) blending abiraterone acetate, niraparib, a wetting agent, and a diluent, optionally in the presence of a disintegrant and a lubricant;

(b) dry-granulating the blend obtained from step (a);

(c) milling the dry-granulated product obtained from step (b);

(d) optionally blending the product obtained from step (c), with a wetting agent, a diluent, a disintegrant, and a glidant.

The present disclosure also relates to a process for preparing certain of the granule compositions disclosed herein, comprising the steps of:

a) blending niraparib with a diluent, optionally in the presence of a disintegrant, a glidant, and a lubricant;
b) dry-granulating the blend obtained from step (a);
c) milling the dry-granulated blend obtained from step (b);
d) preparing a binder solution comprising a wetting agent;
e) blending the binder solution of step (d) with abiraterone acetate and a diluent, optionally in the presence of a disintegrant;
f) wet granulating the blend obtained from step (e);
g) drying the product obtained from step (f);
h) blending the granule blends obtained from steps (c) and (g), optionally in the presence of a wetting agent, a diluent, a disintegrant, a lubricant, and a glidant;

wherein steps d)-g) may be performed before, or in parallel, to steps a)-c).

In an aspect, the obtained granule composition is further compressed into a tablet optionally with a lubricant. In an aspect, the process further comprises preparing a coating suspension and coating the tablet with said suspension.

In an aspect, the obtained granule composition is further dosed into a capsule or sachet, optionally with a diluent.

FIGURES

Fig. 1: Flowchart of a manufacturing process and in-process controls for wet co-granulation of abiraterone acetate and niraparib tosylate monohydrate.

Fig. 2: Flowchart of a manufacturing process and in-process controls for coating tablets comprising abiraterone acetate and niraparib tosylate monohydrate.

Fig. 3: Flowchart of a manufacturing process with dry co-granulation of abiraterone acetate and niraparib tosylate monohydrate and compression into tablets.

Fig. 4: Flowchart of a manufacturing process and in-process controls for dry granulation of niraparib tosylate monohydrate, and blending with granules of abiraterone acetate, the latter prepared by wet granulation.

Fig. 5A: *In vitro* dissolution curves of abiraterone acetate from i) a combination of single agents being one capsule of 100-mg eq. niraparib, in tosylate monohydrate form, and 2 tablets of 250-mg abiraterone acetate; ii) a FDC tablet with the composition of Table 2 (50-mg eq. niraparib, in its tosylate monohydrate form, and 500-mg abiraterone acetate; and a iii) a FDC tablet with

the composition of Table 4 (100-mg eq. niraparib, in its tosylate monohydrate form, and 500-mg abiraterone acetate).

Fig. 5B: *In vitro* dissolution curves of niraparib from i) a combination of single agents being one capsule of 100-mg eq. niraparib, in its tosylate monohydrate form, and 2 tablets of 250-mg abiraterone acetate; ii) a FDC tablet with the composition of Table 2 (50-mg eq. niraparib, in its tosylate monohydrate form, and 500-mg abiraterone acetate); and iii) a FDC tablet with the composition of Table 4 (100-mg eq. niraparib, in its tosylate monohydrate form, and 500-mg abiraterone acetate).

Fig. 6: Loss-on-drying (LOD) profiles for the granulates of the compositions of Table 1 and Table 3.

Fig. 7: Sieve analysis of the granulate of Table 1.

Fig. 8: Sieve analysis of the granulate of Table 3.

DETAILED DESCRIPTION

The present inventions may be understood more readily by reference to the following detailed description, taken in connection with the accompanying examples, which form a part of this disclosure. It is to be understood that these inventions are not limited to the specific products, methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed inventions.

The entire disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference.

Definitions

As employed above and throughout the disclosure, the following terms and abbreviations, unless otherwise indicated, shall be understood to have the following meanings.

In the present disclosure the singular forms “a,”, “an,” and “the” include the plural reference, and reference to a given numerical value includes at least that value, unless the context clearly indicates otherwise. Thus, for example, a reference to “an ingredient” is a reference to one or more of such ingredients and equivalents thereof known to those skilled in the art, and so forth. Furthermore, when indicating that a certain element “may be” X, Y, or Z, it is not intended by such usage to exclude in all instances other choices for the element.

When values are expressed as approximations, by use of the antecedent “about,” it will be understood that the particular value forms another embodiment. As used herein, “about X” (where X is a numerical value) preferably refers to ±10% of the recited value, inclusive. For example, the phrase “about 8” refers to a value of 7.2 to 8.8, inclusive; as another example, the

phrase "about 8%" refers to a value of 7.2% to 8.8%, inclusive. Where present, all ranges are inclusive and combinable. For example, when a range of "1 to 5" is recited, the recited range should be construed as including ranges "1 to 4", "1 to 3", "1-2", "1-2 & 4-5", "1-3 & 5", and the like. In addition, when a list of alternatives is positively provided, such a listing can also include embodiments where any of the alternatives may be excluded. For example, when a range of "1 to 5" is described, such a description can support situations whereby any of 1, 2, 3, 4, or 5 are excluded; thus, a recitation of "1 to 5" may support "1 and 3-5, but not 2", or simply "wherein 2 is not included."

The term "immediate release" when used in the context of dosage forms (such as pharmaceutical formulations, free-dose combinations, fixed-dose combinations, granules, tablets, capsules, and the like), refers to the rapid disintegration and dissolution of said dosage forms to release the active pharmaceutical ingredients comprised in said dosage forms. The immediate release dosage forms dissolve or disintegrate in the stomach within a short period of time, and provide rapid dissolution and absorption of the active pharmaceutical ingredients, which may produce rapid onset of action.

As used herein, and unless otherwise defined, the terms "treat," "treating" and "treatment" include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue, in particular prostate cancer cells or tissue, and the minimization or delay of the spread of cancer, in particular prostate cancer. The minimization or delay of the spread of cancer includes inhibition of the progress of cancer, a reduction in the rate of progress of cancer, or a halt in the rate of progress of cancer.

As used herein, and unless otherwise defined, the phrase "therapeutically effective amount" or "effective amount" means an amount of the therapeutic agent effective for treating a prostate cancer.

As used herein, and unless otherwise defined, the phrase "safe therapeutic" means an amount of the therapeutic agent that is safe for treating a prostate cancer.

The term "pharmaceutically acceptable" means that which is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which are acceptable for human pharmaceutical use as well as veterinary use.

The terms "formulation" and "composition" may be used interchangeably in the present disclosure. Both "formulation" and "composition" refer to at least combining two or more components, either as fixed-dose combinations or as free-dose combinations. As such the term "a pharmaceutical formulation" refers to fixed-dose combinations and free-dose combinations. The two or more components encompass herein at least 1) abiraterone acetate; and 2) niraparib, and any pharmaceutically acceptable salt, solvate, and hydrate forms thereof, for example niraparib tosylate monohydrate. The additional components are usually excipients.

As used herein, a "fixed-dose combination" (FDC) are formulations or compositions that include two or more active ingredients combined in a single dosage form. Herein, the two active ingredients are 1) abiraterone acetate; and 2) niraparib, and any pharmaceutically acceptable salt, solvate, and hydrate forms thereof, for example niraparib tosylate monohydrate.

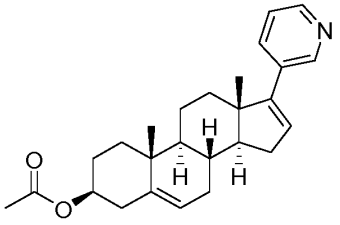
In contrast, a "free-dose combination" (FrDC) are formulations or compositions that include two or more active ingredients combined in separate dosage forms. Herein, the two active ingredients are 1) abiraterone acetate; and 2) niraparib, and any pharmaceutically acceptable salt, solvate, and hydrate forms thereof, for example niraparib tosylate monohydrate.

The terms "excipient" and carrier" are used interchangeably in the present disclosure. The European Pharmacopoeia (Ph. Eur.) defines an excipient as "any component, other than the active substance(s), present in a medicinal product or used in the manufacture of the product. The intended function of an excipient is to act as the carrier (vehicle or basis) or as a component of the carrier of the active substance(s) and, in so doing, to contribute to product attributes such as stability, biopharmaceutical profile, appearance and patient acceptability and to the ease with which the product can be manufactured. Usually, more than one excipient is used in the formulation of a medicinal product." The terms vehicle and basis are further defined in the same pharmacopoeia: "A vehicle is the carrier, composed of one or more excipients, for the active substance(s) in a liquid preparation" and "A basis is the carrier, composed of one or more excipients, for the active substance(s) in semi-solid and solid preparations."

"Granules", "granulate", or "granulated particles" are defined herein as particles containing one or more active pharmaceutical ingredients (API) and at least one pharmaceutically acceptable carrier, that are formed by granulation. A granule composition according to the present disclosure comprises two APIs and at least one pharmaceutically acceptable carrier. A portion of the granule composition, i.e., a first portion of granules, may consist essentially of one API and at least one pharmaceutically acceptable carrier, and another portion of the granule composition, i.e., a second portion of granules, may consist essentially of another API and at least one pharmaceutically acceptable carrier. In another aspect, each and all of the portions of the granule composition, i.e. each and all of the granules, comprise two APIs and at least one pharmaceutically acceptable carrier.

Abiraterone Acetate

Abiraterone acetate is a compound of formula:



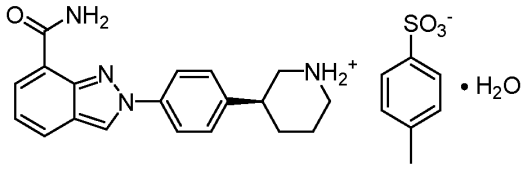
and is a prodrug of abiraterone, which is a potent selective, orally active inhibitor of the key enzyme in testosterone synthesis, 17α-hydroxylase-C17,20-lyase, also known as steroid 17α-monooxygenase inhibitor or Human Cytochrome P45017α. Suppression of testosterone synthesis has been demonstrated with abiraterone acetate in patients with prostate cancer. The compound was disclosed in WO 93/20097 (A1). In some aspects, abiraterone acetate is used herein in crystalline form.

Abiraterone acetate plus prednisone is approved for use in metastatic castration-resistant prostate cancer (mCRPC) and metastatic hormone-sensitive prostate cancer (mHSPC). Abiraterone acetate tablets are currently on the market as 250 or 500 mg oral tablets.

Niraparib

Niraparib, or 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide, is an orally available highly selective poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor, with activity against PARP-1 and PARP-2 deoxyribonucleic acid (DNA)-repair polymerases. The preparation of niraparib is described in U.S. Patent Nos. 8,071,623 and 8,436,185, both of which are incorporated herein by reference.

The currently marketed capsule formulation (ZEJULA) contains 159.4 mg niraparib tosylate monohydrate (equivalent (eq.) to 100 mg niraparib free base) as the active ingredient. The inactive ingredients in the capsule fill include magnesium stearate and lactose monohydrate.



As used herein, the term "niraparib" means any of the free base compound (2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide), a salt form, including pharmaceutically acceptable salts, of 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide (e.g., 4-methylbenzenesulfonic acid; 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide), and/or a solvated form, including a hydrated form, thereof (e.g., 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide tosylate monohydrate). Such forms may be individually referred to as "niraparib free base", "niraparib tosylate" and "niraparib tosylate monohydrate", respectively. Unless otherwise specified, the term "niraparib" includes all crystals, polymorphs, pseudopolymorphs, hydrates, monohydrates, anhydrous forms, solvates, salt forms, and combinations thereof, if applicable, of the compound 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide. Examples of salts include, without being limited to, tosylate or 4-methylbenzenesulfonate, sulfate, benzenesulfate, fumarate, succinate, camphorate, mandelate, camsylate, and lauryl sulfate. In a particular aspect, the term "niraparib" refers to niraparib tosylate monohydrate.

The term "niraparib" also encompasses the amorphous and the crystal polymorphs of this compound, and the hydrates, ansolvates, and solvates thereof. Examples of polymorphs are described in WO 2018/183354 A1, which is incorporated herein by reference. Crystal Form I of 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide tosylate monohydrate is characterized by at least one X-ray diffraction pattern reflection selected from a 2θ value of 9.5±0.2, 12.4±0.2, 13.2±0.2, 17.4±0.2, 18.4±0.2, 21.0±0.2, 24.9±0.2, 25.6±0.2, 26.0±0.2, and 26.9±0.2. Crystal Form II of 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide tosylate non-stoichiometric hydrate is characterized by at least one X-ray diffraction pattern reflection selected from a 2θ value of 9.7±0.3, 12.8±0.3, 17.9±0.3, 19.7±0.3, and 21.8±0.3. Crystal Form III of 2-[4-[(3S)-piperidin-3-yl]phenyl]-2H-indazole-7-carboxamide tosylate anhydrous form is characterized by at least one X-ray diffraction pattern reflection selected from a 2θ value of 17.8±0.2, 19.0±0.2, or 22.8±0.2. Crystal Form I is preferred. More examples of polymorphs are described in WO 2020/072797 A1, which is incorporated herein by reference.

The term "niraparib eq." or "niraparib equivalent" refers to the free base dose amount of niraparib.

Preparation of Dosage Forms

The dosage forms of the present disclosure may be prepared according to the scheme of Figs. 1 and 2. A binder solution comprising purified water, binder (for example hypromellose), and a wetting agent (for example sodium lauryl sulfate) is prepared by mixing with a stirrer/mixer. Abiraterone acetate, niraparib tosylate monohydrate, diluent (for example lactose monohydrate), and disintegrant (for example crospovidone) are screened, blended (blend nr. 1), and added to the binder solution. Wet granulation, including warming, spraying and drying, is performed. Moisture content and particle size distribution are measured for compliance with quality requirements. Following, a mixture of diluent (for example silicified microcrystalline cellulose), disintegrant (for example crospovidone), wetting agent (for example sodium lauryl sulfate), and glidant (for example colloidal anhydrous silica) are screened and blended with the previously obtained granulated material (blend nr. 2). Lubricant (for example magnesium stearate) is screened and added to blend nr. 2, which is finally blended (blend nr. 3), compressed into tablets, and packaged. During compression, the appearance, weight, hardness, thickness, friability, and disintegration of the tablets are measured for compliance with quality requirements.

Following, a coating suspension comprising purified water and a coating powder (for example Opadry® AMB II, for example Opadry® AMB II 88A220039 yellow) is prepared. The previously obtained tablets comprising abiraterone acetate and niraparib tosylate monohydrate are film coated with the coating suspension. Appearance of the obtained coated tablets is

measured for compliance with quality requirements. Tablets are then packaged, e.g., in blister packs or bottles.

In another aspect, the dosage forms of the present disclosure may be prepared as depicted in Fig. 3 and Fig. 2. Abiraterone acetate and niraparib tosylate monohydrate are co-granulated with suitable excipients by means of fluid bed granulation or by means of roller compaction granulation. The granulated material is then compressed into monolayer tablets.

Following, a coating suspension comprising purified water and a coating powder (for example Opadry® AMB II, for example Opadry® AMB II 88A220039 yellow) is prepared. The previously obtained tablets comprising abiraterone acetate and niraparib tosylate monohydrate are film coated with the coating suspension. Appearance of the obtained coated tablets is measured for compliance with quality requirements. Tablets are then packaged, e.g., in blister packs or bottles.

Yet in another aspect, the dosage forms of the present disclosure may be prepared as depicted in Fig. 4 and Fig. 2. Niraparib tosylate monohydrate, a diluent (for example lactose monohydrate and microcrystalline cellulose), a binder (for example povidone K30), a disintegrant (for example crospovidone), a glidant (for example colloidal anhydrous silica), and a lubricant (for example magnesium stearate) are screened, blended, co-milled, blended again, and dry granulated (dry granule composition nr. 1). Abiraterone acetate, a diluent (for example lactose monohydrate), and a disintegrant (for example croscarmellose sodium) are mixed and optionally sieved. A binder solution comprising a binder (for example Hypromellose), a wetting agent (for example sodium lauryl sulfate) and purified water, is prepared and added to the mixture of abiraterone acetate, diluent and disintegrant. Abiraterone acetate granules are then formed by fluid bed granulation and subsequently dried (wet granule composition nr. 2). The wet granule composition nr. 2, a diluent (for example silicified microcrystalline cellulose), a disintegrant (for example crospovidone), a wetting agent (for example sodium lauryl sulfate), and a glidant (colloidal anhydrous silica) is added to the dry granule composition nr. 1, and the resulting mixture is screened and blended. Lubricant (for example magnesium stearate) is added to the previous blend, and the resulting mixture is further screened, blended, compressed into tablets, and packaged. During compression, the properties of the tablets including appearance, weight, hardness, thickness, friability, and disintegration, are measured for compliance with quality requirements. Following, a coating suspension comprising purified water and a coating powder (for example Opadry® AMB II, for example Opadry® AMB II 88A220039 yellow) is prepared. The previously obtained tablets comprising abiraterone acetate and niraparib tosylate monohydrate are film coated with the coating suspension. Appearance of the obtained coated tablets is measured for compliance with quality requirements. Tablets are then packaged, e.g., in blister packs or bottles.

Granulation

Granulation is a process of enlargement of powdered particles to form grain-like agglomerates. The granules formed from the particles of the active pharmaceutical ingredient(s) (API(s)) and excipient mix are further processed effectively into solid dosage forms, such as tablets and capsules, or multiparticulates, such as pellets, beads, or spheroids to be filled into capsules or packed as sprinkle formulations, for example.

Abiraterone acetate and niraparib may be co-granulated. Alternatively, granules of each of 1) abiraterone acetate, and 2) niraparib, may be prepared separately and later mixed or blended, and further processed.

Co-granulation is practically achieved by bringing the two drugs into contact with each other, and with one or more excipients like a binder solution, and subjecting the entire mix to granulation. Alternatively, each of the drugs is brought into contact with one or more excipients creating separate mixes, each of the mixes is then brought together and put into contact with a binder solution.

Abiraterone acetate and niraparib may be dry-granulated or wet-granulated before further processing, like tableting or encapsulating.

In an aspect, abiraterone acetate and niraparib may be co-granulated by wet granulation and further processed. In an aspect, abiraterone acetate and niraparib may be co-granulated by dry granulation and further processed. In an aspect, abiraterone acetate is wet granulated and niraparib is dry granulated and the resulting granules blended and further processed. In an aspect, abiraterone acetate is dry granulated and niraparib is wet granulated and the resulting granules blended and further processed.

Wet granulation

As used herein, the term "wet granulation" refers to the general process of using a granulation liquid in the granulation process to subsequently form granules, as discussed in Remington: The Science and Practice of Pharmacy, 20th Edition (2000), Chapter 45, which is hereby incorporated by reference.

Wet granulation usually includes the steps of mixing; wetting and kneading, i.e., wet massing; granulating; drying; and sieving. These steps are discussed in more detail below.

The wet granulation process begins with the formation of a powder blend of the therapeutic compound or compounds and at least one pharmaceutically acceptable excipient by mixing with, e.g., pharmaceutical granulation equipment, the ingredients (i.e., bringing into intimate proximity) in a suitable container, so as to form a mixture. Examples of pharmaceutical granulation equipment include but are not limited to, shear granulators (e.g., Hobart, Collette, Beken) in combination with an oscillating granulator; high-speed mixers/granulators (e.g., Diosna, Fielder, Collette-Gral); and fluidized-bed granulators (e.g., Aeromatic, Glatt) with a

subsequent sieving equipment. Excipients useful for initially mixing with the therapeutic compound include, e.g., binders, fillers, disintegrants, diluents, wetting agents and any combinations of the foregoing.

The next step is wet massing the powder blend by adding a granulation liquid while agitating or kneading the powder blend until the powder blend is wetted with the granulation liquid to form a wet mass. For example, 10-30% (w/w) granulation liquid is added to the powder blend. Alternatively, 10-25% (w/w), e.g., 20-25%, granulation liquid can be added to the powder blend. The granulation liquid, for example, is pharmaceutically acceptable and volatile. Examples of suitable granulation liquids include, but are not limited to, water, organic solvents (e.g., methanol, ethanol, isopropanol, acetone) either alone or in combination. An example of a combination granulation liquid includes water, ethanol and isopropanol together.

Alternatively, the wet granulation process may begin with the therapeutic compound or compounds as a powder by itself. During wet massing, the granulation liquid that is introduced to the powder is a solvent containing a dissolved excipient, e.g., a binder. Irrespective of how wet-massing takes place, a pharmaceutical composition containing the therapeutic compound and at least one pharmaceutically acceptable excipient is wetted by the granulation liquid. In one example, water is used as the granulation liquid.

The wet mass is optionally sieved forming moist, or damp, granulates. The wet mass, e.g., can be sieved through a mesh, such as a 5, 4, 3, 2, or 1 mm screens, preferably from 1 to 2 mm screen. One of ordinary skill in the art can select the appropriate size of the screen to form the most appropriate granulate size.

Alternatively, a comminuting mill can be used in lieu of the screen or sieve. Examples of a comminuting mill include, but are not limited to, a Stokes oscillator, a Colton rotary granulator, a Fitzpatrick comminuting mill, a Stokes tornado mill.

Also, alternatively, a high-speed mixer equipped with, e.g., a chopper blade, can be used to replace either the screen or the comminuting mill. This, e.g., allows the wet massing, granulating, and the milling to be combined into a single step.

Other wet granulation methods that can be employed include high-shear granulation and twin-screw granulation. High-shear granulation involves adding a binder solution to a powder, which is often a mixture of API(s) and one or more excipients, and granulating the resulting mixture with blending tools and a chopper. The powder agglomerates into larger granules, held together by the binder. Twin screw granulation may be accomplished with twin-screw extruders available in the market such as those manufactured by Leistritz Extrusionstechnik GmbH — NANO 16, Thermo Fisher Scientific — Pharma 16 TSG). The ConsiGma™ system from GEA Pharma Systems is a complete continuous package comprising some or all of blending, twin-screw granulation, drying (semi-continuous), milling and tableting.

The moist granulates, for example, are subsequently dried. For example, the moist granulates can be collected on trays and transferred to a drying oven. Alternatively, the moist granulates can be placed in a drying cabinet with circulating air current and thermostatic heat control. Yet another option is to dry the moist granulates in a fluidized-bed drier. In this example, the moist granulates are suspended and agitated in a warm air stream such that the moist granulates are maintained in motion. For example, the temperature can be from about room temperature to about 90 °C, e.g., 70 °C. The moist granulates are dried to a loss on drying ("LOD") value preferably less than or equal to about 3% or 2%, e.g., less than 2.6%, less than 2%, e.g., 1-2%, by weight of the composition. Drying can take place within or apart from the pharmaceutical granulation equipment.

The granules comprising abiraterone acetate and niraparib tosylate monohydrate, prepared by the wet granulation of the present invention, achieve an improved LOD between 1 and 2%. If the LOD would be too low, the granules could result later in compression problems during tableting. If too high, the granules could have stability issues.

Subsequent to drying, the granulates can be further sieved, i.e., dry screened, alone or in combination with at least one excipient. This typically results in a more uniform particle size of the granulate, preparing the granulates for further processing into a solid oral dosage form. Standard equipment like Quadro comil may be used at a fixed rotational speed (rpm) to screen the dried granules to produce material with desired particle size and free from agglomerates. The rotational speed may be from 5 to 15 rpm, preferably from 8 to 10 rpm.

In one way of preparation by wet granulation, for instance by fluid bed granulation, a binder solution is created by dissolving a binder, wetting agent, and purified water until a clear solution is obtained. The therapeutic compounds, optionally mixed with a diluent and disintegrant are transferred into a suitable wet granulation equipment, and the resulting mass is warmed up while fluidizing. The binder solution is sprayed completely upon the mass using the wet granulation technique. The resulting granulate is dried after spraying while fluidizing. The dried powder is collected and packed in bags, for instance aluminum bags.

In another way of preparation, the therapeutic compound(s) may be wet-granulated in a fluid bed granulator, such as for example, a GEA Sirocco 300 or a Niro Aeromatic D600, resulting in the drug granulates. The inlet air temperature of the fluid bed may vary from 25 °C to 80 °C or from 25 °C to 70 °C, preferably from 25 °C to 65 °C; the outlet air temperature may vary from 25 °C to 50 °C, from 20 °C to 50 °C, or from 25 °C to 80 °C; the inlet air flow may range from 500 to 2200 m^3/h, from 2000 to 3000 m^3/h, from 800 to 1300 m^3/h, or from 500 to 4500 m^3/h; the solution flow rate or spray rate may range depending on the batch size and equipment capacity from 170 to 4200 g/min, from 190 to 300 g/min, from 400 to 900 g/min, or between 0.200 to 2 kg/min; the atomizing air pressure may range from 2-6 bar, from 3 to 4 bar, or from 1.00 to 5.00 bar. In an example, the abiraterone acetate and niraparib or niraparib tosylate

monohydrate may be wet-granulated with a binder solution comprising a solvent, such as for example, water, a binder, such as for example, a polymer, e.g., hypromellose, and a wetting agent, such as for example, sodium lauryl sulfate. In an example, prior to being granulated with a binder solution, the abiraterone acetate may be mixed with a suitable diluent, such as for example, lactose monohydrate, and a suitable disintegrant, such as for example, crospovidone.

Dry granulation

The term "dry granulation" means the process of blending therapeutic compound(s) with at least one excipient. The blend is then compressed, or compacted, to form a compressed material or "compact". This material is then broken apart by crushing, grinding or cutting into dry granulated particles. Optionally, the particles may be further processed, like further mixing with additional excipients. Crushing, grinding, or cutting processes involve an operation that reduces the size of the compressed material such as accomplished by milling or by other operations known to those skilled in the art.

A "compact" is a compressed material formed by processing the therapeutic compound or compounds and optional excipients by slugging or by roller compaction.

For preparing the blend, the components are weighed and placed into a blending container. Blending is performed for a period of time to produce a homogenous blend using suitable mixing equipment. Optionally, the blend is passed through a mesh screen to de-lump the blend. The screened blend may be returned to the blending container and blended for an additional period of time. Lubricant may then be added, and the blend mixed for an additional period of time. The blend is then compressed, or compacted, to form a compact. Prior to compression, the blend may be subjected to a precompression step such as on a rotary tablet press. Compression of the blend to form granules may be accomplished by techniques known in the art including slugging where the blend is introduced into dies comprising one or more punch faces that are installed on a press such as a tablet press and pressure is applied to the blend by the movement of one or more punch faces in the die. Dry granulation may also be performed by means of a roller compactor. A roller compactor generally incorporates two or more rollers adjacent and parallel to each other with a fixed or adjustable gap between the rollers. A hopper or other feeding device deposits blend between the moving rollers which act to compact the blend into a compacted material. Roller compactors are typically equipped with dividers that cut or otherwise divide the compacted material emerging from the roller compactor into ribbons. An example of a roller compactor is TF-Mini Roller Compactor (Vector Corporation, Marion, IA, Freund).

The compact is then broken apart to form granules, typically by suitable mechanical means, such as by crushing, grinding or cutting. For example, granules may be formed from a compact by milling. Milling involves subjecting the granules to a shear force such that the desired

particle size of the granulation is achieved. The milling step may range from an aggressive process where the particle size is reduced significantly to a non-aggressive process where the particle size is not reduced significantly, but merely done to de-lump or break up larger clumps of granulation.

In the pharmaceutical industry, milling is often used to reduce the particle size of solid materials. Many types of mills are available including pin mills, hammer mills and jet mills. One of the most commonly used types of mill is the hammer mill. The hammer mill utilizes a high-speed rotor to which a number of fixed or swinging hammers are attached. The hammers can be attached such that either the knife face or the hammer face contacts the material. As material is fed into the mill, it impacts on the rotating hammers and breaks up into smaller particles. A screen is located below the hammers, which allows the smaller particles to pass through the openings in the screen. Larger particles are retained in the mill and continue to be broken up by the hammers until the particles are fine enough to flow through the screen. The material may optionally be screened. In screening, material is placed through a mesh screen or series of mesh screens to obtain the desired particle size.

Excipients

The formulations of the disclosure, including granules and final dosage forms like tablets, may comprise one or more conventional excipients (pharmaceutically acceptable carrier) such as disintegrants, diluents, binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes. In an aspect, the formulations of the present disclosure include a disintegrant, a diluent or filler, a lubricant and glidant. In an aspect, the formulations of the present disclosure include a disintegrant, a diluent or filler, a lubricant, glidant, a wetting agent and a binder. In an aspect, the formulations of the present disclosure include a disintegrant, a diluent or filler, a lubricant, glidant, a wetting agent and a binder, wherein the wetting agent or part of it, and the binder are present in granules of abiraterone acetate and niraparib. In an aspect, the formulations of the present disclosure include a disintegrant, a diluent or filler, a lubricant, glidant, a wetting agent and a binder, wherein the wetting agent or part of it, the binder, and the disintegrant or part of it, are present in granules of abiraterone acetate and niraparib. In an aspect, the formulations of the present disclosure include a disintegrant, a diluent or filler, a lubricant, glidant, a wetting agent and a binder, wherein the wetting agent or part of it, the binder, the diluent, and the disintegrant or part of it, are present in granules of abiraterone acetate and niraparib. In an aspect, the formulations of the present disclosure include a disintegrant, a diluent or filler, a lubricant, glidant, and a wetting agent, wherein the wetting agent or part of it is present in granules of abiraterone acetate and niraparib.

In an aspect, the formulations of the present disclosure comprise an intragranular phase and an extragranular phase.

In an aspect, the intragranular phase comprises the APIs, a diluent or filler, a disintegrant, a wetting agent, and a binder. In an aspect, the intragranular phase comprises the APIs, a diluent or filler, a disintegrant, a wetting agent, a glidant, and a lubricant.

In an aspect, the extragranular phase comprises a diluent or filler, a disintegrant, a wetting agent, a glidant, and a lubricant.

In an aspect, the intragranular and extragranular phases comprise a disintegrant, e.g., crospovidone. The presence of disintegrant both in the intragranular and extragranular phases improves disintegration of the tablet and the granules, thereby increasing dissolution of the APIs in the body, eventually increasing the bioavailability of the APIs.

Suitable wetting agents may be selected from anionic, cationic or non-ionic surface-active agents or surfactants. Suitable anionic surfactants include those containing carboxylate, sulfonate, and sulfate ions, such as sodium lauryl sulfate (SLS), sodium laurate, dialkyl sodium sulfosuccinates particularly bis-(2-ethylhexyl) sodium sulfosuccinate, sodium stearate, potassium stearate, sodium oleate and the like. Suitable cationic surfactants include those containing long chain cations, such as benzalkonium chloride, bis-2-hydroxyethyl oleyl amine or the like. Suitable non-ionic surfactants include polyoxyethylene sorbitan fatty acid esters, fatty alcohols such as lauryl, cetyl and stearyl alcohols; glyceryl esters such as the naturally occurring mono-, di-, and tri-glycerides; fatty acid esters of fatty alcohols and other alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose, and cholesterol. In an aspect, the wetting agent is sodium lauryl sulfate.

The amount of wetting agent in the tablets or pharmaceutical formulations according to the present disclosure may conveniently range from about 0.5 to about 8% (w/w) and preferably range from about 1 to 7% (w/w) or from about 2 to 6% (w/w) or from about 3 to 6% (w/w). In an aspect, the wetting agent is sodium lauryl sulfate and is present in the final dosage forms in a percentage of about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.85, about 3.9, about 4.00, about 4.07, about 4.1, about 4.2, about 4.3, about 4.4, about 4.5, about 4.6, about 4.7, about 4.8, about 4.9, about 5.0, about 5.1, about 5.2, about 5.3, about 5.4, about 5.5, about 5.6, about 5.7, about 5.8, or about 5.9% by weight.

In an aspect, the wetting agent is sodium lauryl sulfate and is present in the granule composition in a by weight ratio versus abiraterone acetate of about 0.005:1 to 0.02:1 (SLS:abiraterone acetate), preferably about 0.01:1, more preferably about 0.0112:1.

In an aspect, the wetting agent is sodium lauryl sulfate and is present in the final dosage forms in a by weight ratio versus abiraterone acetate of about 0.05:1 to 0.2:1 (SLS:abiraterone acetate), preferably about 0.1:1, more preferably about 0.11:1, about 0.12:1 or about 0.123:1.

Suitable disintegrants are those that have a large coefficient of expansion. Examples of pharmaceutically acceptable disintegrants include, but are not limited to, starches, clays, celluloses, alginates, gums, hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone, e.g., commercially available as Kollidon CL-F and Polyplasdone XL-10) and croscarmellose sodium (crosslinked sodium carboxymethylcellulose). The disintegrant may be present in the tablets or pharmaceutical formulations in an amount from about 1 to about 20% (w/w), preferably from about 2 to about 10% (w/w), in particular from about 3 to 9%, or from about 5 to 9% (w/w).

For the granule compositions of the present invention and the oral dosage forms comprising these granule compositions, excipients that can dissociate into ions are less preferred although an exception is made with sodium lauryl sulfate (wetting agent) and magnesium stearate (lubricant), in the formulations disclosed herein. In particular embodiments, the disintegrant is a non-ionizable disintegrant, such as crospovidone.

A variety of materials may be used as diluents or fillers. Examples are lactose monohydrate, anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g., micro-crystalline cellulose (Avicel™), silicified microcrystalline cellulose), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof (e.g., spray-dried mixture of lactose monohydrate (75%) with microcrystalline cellulose (25%), which is commercially available as MicroceLac®). Preferred is microcrystalline cellulose, silicified microcrystalline cellulose, or lactose monohydrate. Lactose monohydrate is usually characterized as a diluent or filler but it has also binding properties that are particularly useful for the granulation of the intragranular phase. The amount of diluent or filler in the tablets or pharmaceutical formulations according to the present disclosure may conveniently range from about 20% to about 70% (w/w) and preferably ranges from about 20% to about 60% (w/w), or from about 25% to about 35% (w/w), or from about 25% to about 30% (w/w). Preferably the diluent silicified microcrystalline cellulose is used in the extra-granular phase. Preferably a tablet FDC comprises an extragranular phase containing from about 25% to about 30% (w/w) of silicified MCC HD90. This content of silicified MCC HD90 provides an optimal compression profile of the tablet, decreasing its friability and abrasion.

Examples of pharmaceutically acceptable binders include, but are not limited to, starches; celluloses and derivatives thereof, e.g., microcrystalline cellulose, e.g., AVICEL PH from FMC (Philadelphia, PA), hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxylpropylmethyl cellulose, e.g., METHOCEL from Dow Chemical Corp. (Midland, MI); sucrose; dextrose; corn syrup; polysaccharides; and gelatin. The binder, e.g., may be present in an amount from about 0.5% to about 5%, e.g., 0.5 to 3% by weight of the formulation. Preferably the binder is hypromellose of low viscosity grade, e.g., HPMC 2910 15 mPa.s.

Lubricants and glidants can be employed in the manufacture of certain dosage forms and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g., hydrogenated cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, colloidal anhydrous silica talc, mixtures thereof, and others known in the art. Interesting lubricants are magnesium stearate, and mixtures of magnesium stearate with colloidal anhydrous silica. A preferred lubricant is magnesium stearate. A preferred glidant is colloidal anhydrous silica. Glidants generally comprise 0.2 to 5.0% of the total weight of the composition, in particular the total tablet weight, in particular 0.25 to 1.5%, more in particular 0.3 to 1.0% (w/w). Lubricants, like magnesium stearate, generally comprise 0.2 to 5.0% of the total tablet weight, in particular 0.5 to 2.5%, more in particular 0.5 to 2.0%, for example about 1.0%, about 1.25%, or about 1.5% (w/w).

Final Pharmaceutical Formulations

The granulates may be formulated with excipients into oral dosage forms, solid oral dosage forms, tablets, pills, lozenges, caplets, hard or soft capsules, sachets, troches, aqueous or oily suspensions, dispersible powders or granules, granulates.

Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

Tablets contain the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose monohydrate, silicified microcrystalline cellulose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, crospovidone, microcrystalline cellulose, sodium croscarmellose, corn starch, or alginic acid; binding agents, for example, starch, gelatin, polyvinyl-pyrrolidone or acacia; lubricating agents, for example, magnesium stearate, stearic acid or talc; and glidants like colloidal anhydrous silica.

To make, e.g., a tablet, the granules are combined or blended with at least one excipient, e.g., a lubricant, to form a mixture. The blending can be accomplished using any conventional pharmaceutical equipment, e.g., a V-blender.

Furthermore, any additional excipients used can be sieved separately from the granules or concurrently with the sieving of the granules as described in the afore-mentioned dry sieving step. One of ordinary skill in the art will appreciate the necessary particle size of each component that is necessary for the particular pharmaceutical composition being formulated.

The blended mixture can, e.g., be subsequently compacted into a tablet (e.g., by using a tablet press) or encapsulated into a capsule. The tablet hardness is preferably in a range of 250 to 350 N. The solid oral dosage forms may be subject to further conventional processing as known to one of ordinary skill in the art, e.g., imprinting, embossing or coating.

The tablets may be uncoated or they may be coated by known techniques. Tablets of the present disclosure may further be film-coated e.g. to improve taste, to provide ease of swallowing and an elegant appearance. Many suitable polymeric film-coating materials are known in the art. In an aspect, the film-coating material is Opadry® AMB II 88A170010 beige, Opadry® AMB II 88A210027 green, Opadry® AMB II 88A620004 yellow, Opadry® AMB II 88A220039 yellow, Opadry® QX 321A220006 yellow, or Opadry® II 32F220009. The film-coating material is usually mixed with purified water Ph. Eur to form a coating suspension. Preferred coating suspensions are those in which the film-coating material is Opadry® AMB II 88A170010 beige, Opadry® AMB II 88A210027 green, and Opadry® AMB II 88A620004 yellow, because the resulting coated tablets show no scuffing. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, hydroxypropyl methylcellulose (HPMC), especially HPMC 2910 5 mPa.s, and acrylate-methacrylate copolymers. A preferred film-coating material is a water permeable film-coating material, such as for example the HPMC coating Opadry II 32F220009. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g., propylene glycol) and optionally a pigment (e.g., titanium dioxide). The film-coating suspension may also contain talc as an anti-adhesive. In tablets according to the present disclosure, the film coat in terms of weight preferably accounts for about 5% (w/w) or less of the total tablet weight.

In order to facilitate the swallowing of such a formulation by a mammal, it is advantageous to give the formulations, in particular tablets, an appropriate shape. A film coat on the tablet may further contribute to the ease with which it can be swallowed. In an aspect of the present disclosure the tablet may be an oblong shaped tablet, in particular an oblong shaped tablet with a length of $\leq$ 19 mm.

Other excipients such as coloring agents and pigments may also be added to the formulations of the present disclosure. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the formulation of the present disclosure, but when used the coloring agent can be present in an amount from about 1 to about 6% by weight based on the total tablet weight, for example from about 2 to about 5%, from about 3 to about 4%, or up to 3.5% by weight based on the total tablet weight.

Flavors are optional in the formulation and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, or thyme oil. Also useful as flavors are vanilla, citrus oil,

including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth, The amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally, the flavor will be present in an amount from about 0% to about 3% (w/w).

Formulations for oral use may also be presented as hard gelatin or HPMC capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are mixed with water soluble carrier or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the granules with the therapeutic compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanal, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the granules with the therapeutic compounds in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredients in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

At first instance, with the present disclosure pharmaceutical formulations for oral administration such as tablets and capsules are envisaged, but the pharmaceutical formulations of the present disclosure can also be used for rectal administration. Preferred formulations are those adapted for oral administration shaped as a tablet. They can be produced by conventional tableting techniques with conventional ingredients or excipients (pharmaceutically acceptable carrier) and with conventional tableting machines.

Methods of Treatment and Medical Uses

The methods for treating a prostate cancer, or the medical uses of the pharmaceutical formulations comprise, consist of and/or consist essentially of, administering to a patient in need thereof a therapeutically effective amount of the PARP inhibitor niraparib, a therapeutically effective amount of the CYP17 inhibitor abiraterone acetate, and optionally a therapeutically effective amount of another drug, for example a glucocorticoid, for example prednisone.

The methods for treating a prostate cancer, or the medical uses of the pharmaceutical formulations comprise, consist of and/or consist essentially of, administering to a patient in need thereof a free-dose combination (FrDC) or fixed-dose combination (FDC) of niraparib and abiraterone acetate. The methods for treating a prostate cancer, or the medical uses of the pharmaceutical formulations comprise, consist of and/or consist essentially of, administering to a patient in need thereof the afore-mentioned free-dose combination or fixed-dose combination, plus a glucocortidoid, for example prednisone.

The methods of treatment and medical uses disclosed herein comprise administering to a patient in need thereof, oral dosage forms as defined in the present disclosure, said oral dosage forms comprising a granule composition comprising abiraterone acetate, niraparib, and a pharmaceutically acceptable carrier. These oral dosage forms and granule compositions constitute the FDCs.

Also disclosed are dosage regimens of the oral dosage forms disclosed herein, said dosage regimens comprising, consisting of and/or consisting essentially of, administering the FDC of niraparib and abiraterone acetate, and optionally plus a glucocorticoid, for example prednisone, in a total amount that is therapeutically effective for the treatment of prostate cancer in a human patient.

The present disclosure also discloses kits comprising, consisting of, and/or consisting essentially of, a free-dose combination or a fixed-dose combination comprising niraparib and abiraterone acetate, and an instruction print for administering the free-dose combination or fixed-dose combination to a human patient having a prostate cancer.

The kits may comprise, consist, and/or consist essentially of, a free-dose combination or a fixed-dose combination comprising niraparib and abiraterone acetate, a separate composition that comprises a glucocorticoid, for example prednisone; and an instruction print for administering the free-dose combination or fixed-dose combination to a human patient having a prostate cancer.

Where a particular reference is made "prednisone" in the present disclosure, one of ordinary skill will recognize that prednisone may be substituted with a different glucocorticoid, such as prednisolone, hydrocortisone, methyl prednisolone, or dexamethasone. The person skilled in the art will know how to exchange prednisone with these other drugs and adjust their dosage, if necessary.

Particular suitable glucocorticoids include but are not limited to, (1) dexamethasone (e.g., Decadron, oral; Decadron-LA injection, etc.), (2) prednisolone (e.g., Delta-CORTEF®, prednisolone acetate (ECONOPRED®), prednisolone sodium phosphate (HYDELTRASOL®), prednisolone tebutate (HYDELTRA-TBA®, etc.)), (3) prednisone (DELTASONE®, etc.), or (4) methylprednisolone (e.g., MEDROL®), and combinations thereof. See, e g., Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th edition 2001.

The formulations described herein may be used in methods of treating prostate cancer patients with negative biomarker status. The formulations described herein may be used in methods of treating prostate cancer patients with positive biomarker status.

The formulations described herein may be used in methods of treating prostate cancer patients with homologous recombination deficiency (HRD) positive biomarker status. HRD is also referred to as homologous recombination repair (HRR) defects and can result from DNA repair gene defects (DRD). Said HRD –or HRR defects– positive status may be detected by evaluating somatic or germline alterations, or by evaluating genome-wide loss of heterozygosity (LOH), or homozygous deleterious changes in DNA repair genes. HRD –or HRR defects– positive status is also a synonym for PARP biomarker positive status.

The positive biomarker status may be HRD-positive status. The negative biomarker status may be HRD-negative status. HRD status may be evaluated by either a plasma- (Resolution Bioscience) or tissue-based test (Foundation Medicine), particularly by detecting circulating plasma DNA or circulating tumor cells. HRD positive status may be defined as having monoallelic or biallelic alterations in one or more DNA repair genes, including without being limited to, BRCA1 (Breast Cancer gene 1), BRCA2 (Breast Cancer gene 2), ATM (ataxia-telangiectasia mutated), FANCA (Fanconi Anemia Complementation Group A gene), PALB2 (Partner and Localizer of BRCA2 gene), CHEK2 (Checkpoint Kinase 2 gene), BRIP1 (BRCA1 Interacting Protein C-terminal Helicase 1 gene), HDAC2 (Histone deacetylase 2), CDK12 (Cyclin Dependent Kinase 12), RAD51B (RAD51paralog B), RAD54L (RAD54-Like),

CDK17 (Cyclin Dependent Kinase 17), or PPP2R2A (protein phosphatase 2 regulatory subunit B alpha).

Gene expression profile analysis and protein biomarkers may also be used to risk-stratify patients with prostate cancer to guide treatment decisions. Commercially available tests include Prolaris® (Myriad Genetics, Salt Lake City, UT); OncotypeDx® Prostate Cancer Assay (Genomic Health, Redwood City, CA); ProMark™ Protein Biomarker Test/ProMark™ Risk Score (Metamark Genetics, Cambridge, MA); FoundationOne® CDx (Foundation Medicine, Cambridge, MA); FoundationOne® Liquid CDx (Foundation Medicine, Cambridge, MA); Caris Molecular Intelligence (Caris Life Sciences, Irving, TX); Guardant360 (Guardant Health Inc., Redwood City, CA); ProstateNext® (Ambry Genetics, Aliso Viejo, CA); Color Hereditary Cancer Test (Color Genomics, Burlingame, CA); Invitae Prostate Cancer Panel (Invitae Corp., San Francisco, CA); Prostate Gene (GeneHealth, Cambridge, UK); Myriad myRisk® Hereditary Cancer Test (Myriad Genetics Inc., Salt Lake City, UT) and Decipher® Prostate Cancer Test (GenomeDx Biosciences, San Diego, CA), this latter based on the expression pattern of 22 RNA markers in biopsy or radical prostatectomy specimens. Prolaris®, OncotypeDx®, and Decipher® are tissue-based gene expression tests.

The formulations described herein may be used in methods of treating prostate cancer patients with biochemical recurrence (BCR) or biochemical failure (BF). BCR or BF may be defined by a rise in prostate-specific antigen (PSA) without evidence of disease on imaging. For patients who have received primary radiotherapy, BCR is currently defined as a PSA rise of $\geq$ 2.0 ng/mL above the nadir ("Phoenix criteria"). For patients who have received primary surgery, BCR is currently defined as a confirmed PSA rise of $\geq$ 2.0 ng/mL above the nadir.

Next generation imaging (NGI), e.g. prostate-specific membrane antigen positron emission tomography (PSMA-PET), may be used to detect lesions not visible on conventional imaging or below the Phoenix threshold, i.e. PSA rise < 2.0 ng/mL. NGI may for instance classify some patients with localized prostate cancer, BCR, nmCRPC, or nmHRPC as having metastatic prostate cancer.

The formulations described herein may be used in methods of treating prostate cancer patients with BCR or BF, and which are HRD biomarker positive and/or high risk. The HRD biomarker positive may be at least one of BRCA1, BRCA2, ATM, BRIP1, CDK12, CDK17, CHEK2, FANCA, HDAC2, PALB2, PPP2R2A, RAD51B, and RAD54L.

The formulations described herein may be used in methods of treating BCR or BF, oligometastatic disease, or localized prostate cancer in a patient, which may be detected by conventional imaging.

The formulations described herein may be used in methods of treating BCR or BF, oligometastatic disease, or localized prostate cancer in a patient, which may be detected by NGI.

The formulations described herein may be used in methods of treating patients with locally advanced prostate cancer who are candidates for primary radiotherapy.

The formulations described herein may be used in methods of treating cancer patients, particularly CRPC patients, with circulating tumor cells testing negative for the androgen receptor splice variant 7 (AR-V7). The formulations described herein may be used in methods of treating cancer patients, particularly CRPC patients, with circulating tumor cells testing positive for the androgen receptor splice variant 7 (AR-V7).

The formulations described herein may be used in methods of treating prostate cancer in patients with detectable circulating tumor cells (CTC), circulating DNA, or reduction of plasma DNA. The formulations described herein may be used in methods of treating metastatic prostate cancer in patients with detectable CTCs and/or measurable and non-measurable bony disease or lesions. CTC clearance in patients with metastatic prostate cancer may be established when detecting $\geq$5 cells per 7.5 mL blood at baseline, detecting <5 cells per 7.5 mL blood at nadir, further confirmed by a second consecutive value obtained 4 or more weeks later.

The free-dose combinations or fixed-dose combinations of abiraterone acetate and niraparib, and optionally a separate composition that comprises a glucocorticoid, for example prednisone, may be administered to a subject, a patient, a mammal, in particular a human, suffering from prostate cancer, primary peritoneal cancer, breast cancer, or ovarian cancer. In one aspect, the human suffering from breast cancer or ovarian cancer is a biomarker-positive patient.

The prostate cancer may be metastatic prostate cancer, advanced prostate cancer, regional prostate cancer, locally advanced prostate cancer, localized prostate cancer, non-metastatic prostate cancer, non-metastatic advanced prostate cancer, non-metastatic regional prostate cancer, non-metastatic locally advanced prostate cancer, non-metastatic localized prostate cancer, hormone-naïve prostate cancer, chemotherapy-naïve prostate cancer, castration-naïve cancer with or without metastases, radiation-naïve prostate cancer, castration-resistant prostate cancer (CRPC), CRPC with DRD, non-metastatic CRPC (nmCRPC), nmCRPC in a patient population with a PSA doubling time equal to or less than 10 months and are HRD positive (or biomarker enriched), nmCRPC in patients having DRD or HRD, nmCRPC in patients having no DRD, nmCRPC in patients with high-risk BCR (e.g. in a DRD+ population), nmCRPC in patients being monitored with new generation imaging techniques (NGI), localized CRPC, locally advanced CRPC, regional CRPC, advanced CRPC, metastatic CRPC (mCRPC), mCRPC in patients having biallelic DNA-repair gene defect (DRD); mCRPC in patients having monoallelic DRD; mCRPC in patients having no DRD; mCRPC in patients having DRD and having received taxane and/or androgen receptor-targeted therapy, CRPC in patients having received hormone therapy (for example enzalutamide, darolutamide, apalutamide), CRPC in patients having received taxane therapy (for example docetaxel, mitoxantrone, cabazitaxel), chemotherapy-naïve CRPC, chemotherapy-naïve mCRPC, hormone-naïve CRPC, hormone-

naïve mCRPC, CRPC with progression, CRPC with visceral metastases, CRPC with visceral metastases in patients having received hormone therapy (for example enzalutamide, darolutamide, apalutamide), CRPC with visceral metastases in patients having received taxane therapy (for example docetaxel, mitoxantrone, cabazitaxel), CRPC with visceral metastases and progression, castration-sensitive prostate cancer (CSPC), non-metastatic CSPC (nmCSPC), localized CSPC, locally advanced CSPC, regional CSPC, advanced CSPC, metastatic CSPC (mCSPC), chemotherapy-naïve CSPC, chemotherapy-naïve mCSPC, hormone-naïve CSPC, hormone-naïve mCSPC, hormone-sensitive prostate cancer (HSPC), hormone-dependent prostate cancer, androgen-dependent prostate cancer, androgen-sensitive prostate cancer, biochemically relapsed HSPC, metastatic HSPC (mHSPC), hormone-resistant prostate cancer (HRPC), non-metastatic HRPC (nmHRPC), localized HRPC, locally advanced HRPC, regional HRPC, advanced HRPC, metastatic HRPC (mHRPC), recurrent prostate cancer, prostate cancer with prostate specific antigen (PSA) persistence or recurrence after prostatectomy with or without distant metastases, radiation-resistant prostate cancer, and any combination thereof.

The subject or patient may be in a risk group selected from very low risk, low risk, intermediate favorable risk, intermediate unfavorable risk, high risk, very high risk, and regional risk.

The subject may be surgically castrated or chemically castrated.

Most, but not all, prostate cancers are adenocarcinomas, and the patient may have adenocarcinoma or sarcoma-based prostate cancer. In any of these instances, the prostate cancer may be metastatic.

The patient may have undergone one or more other types of treatment for the prostate cancer prior to the first dose of the free-dose combination or fixed-dose combination of niraparib and abiraterone acetate. For example, the patient may have undergone taxane-based chemotherapy prior to administering the free-dose combination or fixed-dose combination of niraparib and abiraterone acetate. Additionally or alternatively, the patient may have undergone at least one line of androgen receptor-targeted therapy, such as apalutamide (ERLEADA®) and/or enzalutamide (XTANDI®), prior to administering the free-dose combination or fixed-dosed combination of niraparib and abiraterone acetate. In an aspect, the patient does not respond initially or becomes refractory to previous treatments, prior to administering the free-dose or fixed-dosed combination of niraparib and abiraterone acetate. Optionally the glucocorticoid, for example prednisone, can also be administered in addition to the free-dose or fixed-dose combination of niraparib and abiraterone acetate.

The period of time between the end of the other treatment and the administration of the free-dose or fixed-dose combination of niraparib and abiraterone acetate, and optionally plus a glucocorticoid, for example prednisone, in accordance with the present disclosure may be years, months, weeks, days, a single day, or less than 24 hours.

The administration of the free-dose or fixed-dose combination of niraparib and abiraterone acetate, and optionally plus a glucocorticoid, for example prednisone, may be on a once, twice or thrice daily basis.

The daily administration includes administering a single fixed-dose combination (FDC) of niraparib and abiraterone acetate, to the patient one, two or three times per day. Any dosage regimen that is embraced by the preceding description is contemplated. In an aspect, 1 tablet or capsule comprising the FDC of niraparib and abiraterone acetate is administered once daily. In an aspect, 2 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily. In an aspect, 3 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily. In an aspect, 1 tablet or capsule comprising the FDC of niraparib and abiraterone acetate is administered once daily, at least 1 hour before a meal or at least two hours after a meal. In an aspect, 2 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily, at least 1 hour before a meal or at least two hours after a meal. In an aspect, 3 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily, at least 1 hour before a meal or at least two hours after meal. In an aspect, 1 tablet or capsule comprising the FDC of niraparib and abiraterone acetate is administered once daily, with water, on an empty stomach at least 1 hour before a meal or at least two hours after meal. In an aspect, 2 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily, with water, on an empty stomach at least 1 hour before a meal or at least two hours after meal. In an aspect, 3 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily, with water, on an empty stomach at least 1 hour before a meal or at least two hours after a meal.

In an aspect a glucocorticoid is administered once or twice daily. In an aspect prednisone tablets or capsules are administered once or twice daily.

In an aspect, 1 or 2 tablets or capsules comprising the FDC of niraparib and abiraterone acetate are administered once daily and 1 tablet or capsule of a glucocorticoid, for example prednisone is administered once or twice daily.

The amount of niraparib equivalent that is administered to the patient may be about 30 to about 400 mg/day, about 50 to about 350 mg/day, about 66 to about 325 mg/day, about 100 to about 300 mg/day, about 100 to about 275 mg/day, about 125 to about 250 mg/day, about 150 to about 225 mg/day, about 175 to about 225 mg/day, or about 190 to about 210 mg/day, or, about 30, about 33, about 40, about 50, about 60, about 66, about 67, about 70, about 80, about 90, about 99, about 100, about 110, about 120, about 130, about 132, about 134, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 201, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, about 310, about 320, about 330, about 340, or about 350 mg/day.

The amount of abiraterone acetate that is administered to the patient may be about 300 to about 2000 mg/day, about 500 to about 1500 mg/day, about 700 to about 1200 mg/day, about 800 to about 1200 mg/day, about 900 to about 1100 mg/day, about 950 to about 1050 mg/day, or may be about 300, about 333, about 500, about 600, about 666, about 700, about 750, about 800, about 850, about 875, about 900, about 925, about 950, about 999, about 1000, about 1025, about 1050, about 1075, about 1100, about 1125, or about 1500 mg/day.

The amount of prednisone that is administered to the patient may be about 1 to about 25 mg/day, about 2 to about 23 mg/day, about 3 to about 20 mg/day, about 4 to about 18 mg/day, about 5 to about 15 mg/day, about 6 to about 12 mg/day, about 7 to about 11 mg/day, about 8 to about 11 mg/day, about 9 to about 11 mg/day, or may be about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, or about 25 mg/day. In some aspects, the patient has mCSPC and the amount of prednisone is 5 mg/day. In some aspects, the patient has mCRPC and the amount of prednisone is 10 mg/day.

When the FDC of niraparib and abiraterone acetate are administered to a patient, the selected dosage level for each drug will depend on a variety of factors including, but not limited to, the activity of the particular compound, the severity of the individual's symptoms, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of niraparib, the amount of abiraterone acetate, and optionally the amount of prednisone, will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

The FDCs may comprise, for example, about 33 to about 350 mg of the niraparib, about 100 to about 1500 mg of the abiraterone acetate.

For example, the instant compositions may include niraparib equivalent in an amount of, for example, 33 to about 350 mg, about 33 to about 300 mg, about 50 to about 200 mg, about 50 to about 150 mg, about 50 to about 100 mg, about 33 to about 100 mg, or may be about 30, about 33, about 50, about 67, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, about 310, about 320, about 330, about 340, or about 350 mg. The instant compositions may include niraparib equivalent in an amount of about 33, about 50, about 67, or about 100 mg.

The instant compositions may also include abiraterone acetate in an amount of, for example, about 100 to about 1500 mg, about 125 to about 1400 mg, about 150 to about 1300 mg, about

175 to about 1200 mg, about 200 to about 1175 mg, about 225 to about 1150 mg, about 250 to about 1100 mg, about 250 to about 1075 mg, about 250 to about 1050 mg, about 250 to about 1000 mg, about 300 to about 950 mg, about 350 to about 900 mg, about 400 to about 850 mg, about 450 to about 800 mg, or about 500 to about 700 mg, or may be about 100, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, about 1000, about 1050, about 1100, about 1150, about 1200, about 1250, about 1300, about 1350, about 1400, about 1450, or about 1500 mg. The instant compositions may include abiraterone in an amount of about 333 or about 500 mg.

The instant compositions may include niraparib equivalent in an amount of about 33 mg and abiraterone in an amount of 333 mg. The instant compositions may include niraparib equivalent in an amount of about 67 mg and abiraterone in an amount of 333 mg. The instant compositions may include niraparib equivalent in an amount of about 50 mg and abiraterone in an amount of 500 mg. The instant compositions may include niraparib equivalent in an amount of about 100 mg and abiraterone in an amount of 500 mg.

The present treatment regimens may also include the separate administration of a glucocorticoid, for example prednisone, in an amount of, for example, about 2 about 15 mg, about 2 to about 14, about 3 to about 13, about 4 to about 12, about 5 to about 11, about 5 to about 10, about 6 to about 11, about 7 to about 11, about 8 to about 11, about 9 to about 11, or may be about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, or about 15 mg.

The present methods may include administering the FDC of niraparib and abiraterone acetate, and optionally the glucocorticoid or prednisone separately, to the patient over multiple days, weeks, months or years. Preferably, the administration of the FDC of niraparib and abiraterone acetate, occurs on a once, twice or thrice daily basis, and optionally the separate administration of the prednisone occurs on a once, twice, or thrice daily basis. The amount of the niraparib, the abiraterone acetate, and optionally the separately-administered prednisone may be constant over time (i.e., from day to day), or may be increased or decreased over time. For example, the amount of niraparib, the abiraterone acetate, and optionally the separately-administered prednisone, or two or all three of these, that is administered per day may be increased or decreased after one day of administration, after a few days of administration, after a week of administration, and the new dosage amount may be maintained for any desired period of time, e.g., days, weeks, or months, or may subsequently be increased or decreased after the desired interval. In this manner, the present methods may include increasing or decreasing the dosing of the FDC of niraparib and abiraterone acetate (e.g.., the amount of niraparib and abiraterone acetate, respectively, that is administered on a once daily basis) at least once over time. The present methods may also or alternatively include increasing or decreasing the dosing of

prednisone (e.g.., the total amount of the prednisone that is administered on a daily basis) at least once over time. The amount of increase or decrease may be expressed in terms of a percentage, and under such circumstances the amount of a single episode of increase or decrease may be about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 80%, about 85%, about 90%, about 95%, about 100%, or by greater than about 100%.

Described herein are methods for treating a cancer in which a therapeutically effective amount of niraparib, abiraterone acetate, and optionally the separately-administered glucocorticoid, such as prednisone, a prednisolone, hydrocortisone, methylprednisolone, and dexamethasone, are administered to a patient, e.g., a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent (for example docetaxel, mitoxantrone, cabazitaxel, cisplatin, carboplatin, oxaliplatin, and etoposide), an immunotherapeutic agent (for example pembrolizumab, sipuleucel-T), bone-targeted therapies (for example denosumab, zoledronic acid, alendronate, radium-223, strontium-89, samarium-153), gonadotropin releasing hormone agonists (GnRHa, including, without being limited to, triptorelin, nafarelin, goserelin, leuprorelin or leuprolide, histrelin, gonadorelin, and buserelin), and hormone therapies (for example nilutamide, flutamide, bicalutamide, goserelin, histrelin, leuprolide, triptorelin, degarelix, enzalutamide, apalutamide, darolutamide, ketoconazole, diethylstilbestrol, estrogens). Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, the methods may be directed to treating a chemotherapy-resistant prostate cancer in a patient, in which a therapeutically effective amount of niraparib and abiraterone acetate is administered to a patient currently receiving an anti-cancer agent.

Additionally, the methods for treating a cancer described herein may be combined with androgen deprivation therapy (ADT). The methods for treating a cancer described herein may be combined with radiation therapy, preferably in an HRD+ population. In an aspect, the methods for treating a cancer described herein may be combined with ADT and external beam radiation therapy (EBRT). The methods for treating a cancer described herein may be combined with alternative energy sources such as high-intensity focused ultrasound (HIFU), cryosurgery, and laser treatments.

The FDC of the present invention, and a separately administered glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone; preferably prednisone or a prednisolone) may be administered to a patient having metastatic prostate cancer. In particular, the FDC of the present invention, and a separately-administered glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone; preferably prednisone or a prednisolone) may be administered to a patient

having mCRPC, such as first-line (L1) mCRPC (e.g., subjects who have not been treated with any therapy in the metastatic castrate-resistant setting, except for androgen deprivation therapy (ADT) and a limited exposure to abiraterone acetate plus prednisone). The patient may be positive for HRD or not positive for HRD. Preferably the patient is positive for HRD. The metastatic prostate cancer may be confirmed by positive bone scan or metastatic lesions on computed tomography (CT) or magnetic resonance imaging (MRI). The patient may have castrate levels of testosterone ≤ 50 ng/dL and may be under GnRHa therapy or has undergone bilateral orchiectomy. The patient may continue with GnRHa therapy during the treatment if not surgically castrated. The patient may have an Eastern Cooperative Oncology Group Performance Score (ECOG PS) Grade of 0 or 1.

ADT uses surgery or medicines to lower the levels of androgens made in the testicles, to stop them from fueling prostate cancer cells. ADT includes, without being limited to, surgical castration or orchiectomy; and medical castration like luteinizing hormone-releasing hormone (LHRH) agonists, e.g., leuprolide, goserelin, triptorelin, histrelin; LHRH antagonists; abiraterone acetate; ketoconazole; anti-androgens like flutamide, bicalutamide, nilutamide, enzalutamide, apalutamide, darulotamide; or estrogens.

The FDC of the present invention, and a separately-administered glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone; preferably prednisone or a prednisolone) may be administered to a patient having mCSPC, e.g., deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCSPC. The deleterious germline or somatic HRR gene mutation may be at least one of, without being limited to, BRCA1, BRCA2, ATM, BRIP1, CDK12, CDK17, CHEK2, FANCA, HDAC2, PALB2, PPP2R2A, RAD51B, and RAD54L. The mCSPC may be confirmed by at least one bone lesion(s) on bone scan; the bone metastasis preferably further confirmed by CT or MRI. The mCSPC may be detected by NGI like PSMA-PET. The patient may have an Eastern Cooperative Oncology Group Performance Score (ECOG PS) Grade of less than or equal to 2. The patient may be under androgen deprivation therapy (either medical or surgical castration) and this therapy may have been started within 6 months prior to the FDC plus prednisone (or a prednisolone) treatment, preferably it may have been started at least 14 days prior to the treatment with the FDC plus prednisone (or a prednisolone). Said androgen deprivation therapy may be continued through the FDC plus prednisone (or a prednisolone) treatment. Those patients who have started GnRHa therapy less than 28 days prior to the FDC plus prednisone (or a prednisolone) treatment, preferably are administered a first-generation anti-androgen, preferably for at least 14 days prior to the FDC plus prednisone (or a prednisolone) treatment. Said anti-androgen must be discontinued prior to the start of the FDC plus prednisone (or a prednisolone) treatment. The patient may have received prior docetaxel or cabazitaxel treatment; preferably the patient has received a maximum of 6 cycles of docetaxel therapy; preferably the patient has received the last dose of docetaxel or cabazitaxel within 2 months

prior the FDC plus prednisone (or a prednisolone) treatment. Prior to FDC plus prednisone (or a prednisolone) therapy, the patient may have received radiation or surgical intervention to manage symptoms of prostate cancer. Prior to FDC plus prednisone (or a prednisolone) therapy, the patient may have received abiraterone acetate plus glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone), preferably during a month prior to FDC plus prednisone (or a prednisolone) therapy. Prior to FDC plus prednisone (or a prednisolone) therapy, the patient may have received treatments for localized prostate cancer, preferably these treatments must have been completed at least 1 year prior to the FDC plus prednisone (or a prednisolone) treatment; for example the patient may have undergone up to 3 years of androgen deprivation therapy; for example the patient may have received radiation therapy, prostatectomy, lymph node dissection, or systemic therapies.

The FDC of the present invention, and a separately administered glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone; preferably prednisone or a prednisolone) may be administered to a patient having metastatic castration-resistant prostate cancer (mCRPC), with or without homologous recombination deficiency (HRD) or DRD, and optionally with cyclin dependent kinase 12 (CDK12) pathogenic alterations. The FDC may be low strength: 100 mg eq. niraparib/1000 mg abiraterone acetate, given as 2 x FDC tablets (50 mg eq. niraparib/500 mg abiraterone acetate), administered orally as a single dose under modified fasted conditions. The FDC may be regular strength: 200 mg eq. niraparib/1000 mg abiraterone acetate, given as 2 x FDC tablets (100 mg eq. niraparib/500 mg abiraterone acetate), administered orally as one daily dose under modified fasted conditions. The patient may be able to continue GnRHa therapy during the FDC plus prednisone (or a prednisolone) treatment if not surgically castrated (i.e, subjects who has not undergone bilateral orchiectomy). The patient may have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of less than or equal to 1. Prior to the FDC plus prednisone (or a prednisolone) treatment, the patient may have been exposed to anti-androgens including, without being limited to, nilutamide, flutamide, bicalutamide, enzalutamide, apalutamide, darolutamide, or abiraterone acetate; preferably said prior anti-androgen therapy is appropriately washed-out before administering the first dose of FDC plus prednisone or a prednisolone. In the case of bicalutamide, flutamide, and nilutamide, the wash-out time is about 2 weeks. For enzalutamide, the wash-out time is about 8 weeks. For apalutamide, the wash-out time is about 6 weeks.

The FDC of the present invention, and a separately administered glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone; preferably prednisone or a prednisolone) may be administered further in combination with leuprorelin acetate (a.k.a. leuprolide acetate), prior to, during, and after radiotherapy, to a patient having high risk and lymph node positive prostate cancer. The radiotherapy may be stereotactic body

radiotherapy (SBRT) or ultra-hypofractionated radiotherapy, with a total dose of about 37.5 to 40 Gy.

The FDC of the present invention, and a separately administered glucocorticoid (e.g., prednisone, a prednisolone, hydrocortisone, methylprednisolone, or dexamethasone; preferably prednisone or a prednisolone) may be administered to a patient having castration-naïve prostate cancer, with or without metastases. The patient may be able to continue GnRHa therapy during the FDC plus prednisone (or a prednisolone) treatment if not surgically castrated (ie, subjects who have not undergone bilateral orchiectomy).

In the disclosed compositions, the niraparib may be present in an amount that is therapeutically effective by itself, the abiraterone acetate may be present in an amount that is therapeutically effective by itself, and optionally the separately-administered prednisone may be present in an amount that is therapeutically effective by itself, or two or more of these conditions may apply. In other examples, the total amount of the niraparib, the abiraterone acetate, and optionally the separately-administered prednisone when considered together may represent a therapeutically effective amount, i.e., the amount of niraparib would not be therapeutically effective by itself, the amount of abiraterone acetate would not be therapeutically effective by itself, and if present, the amount of prednisone would not be therapeutically effective by itself.

Also disclosed herein are kits including a composition that comprises niraparib and abiraterone acetate, and optionally a composition that comprises prednisone, and, an instruction print for administering the compositions to a human patient having prostate cancer. The instruction print may provide instructions for administering the respective compositions once daily, twice daily, or multiple-times daily. For example, the instruction print may provide instructions for administering the composition comprising niraparib and abiraterone acetate to a human patient having prostate cancer on a once daily basis, and optionally for administering the composition comprising prednisone to the human patient on a twice daily basis.

The present disclosure further relates to a method for determining the bioequivalence of a test fixed-dose combination (FDC) formulation of niraparib and abiraterone acetate, relative to an oral dosage form of the present disclosure, said method comprising i) measuring a bioequivalence parameter of the test FDC formulation and optionally measuring a bioequivalence parameter of the oral dosage form of the present disclosure, and ii) comparing the bioequivalence parameter of the test FDC formulation to the corresponding bioequivalence parameter of the oral dosage form of the present disclosure.

In an aspect, the bioequivalence parameter is selected from $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, C_{max} and t_{max}, $AUC_{(0-72h)}$, terminal rate constant (λ_z), $t_{1/2}$, $AUC_{(0-\tau)}$, $C_{max,ss}$, $t_{max,ss}$, $Ae_{(0-t)}$, and R_{max}, which bioequivalence parameters are well known to the person skilled in the arts of bioequivalence and pharmacokinetics.

The present invention is further defined in the following examples. It should be understood that these examples, while indicating preferred embodiments of the invention, are given by way of illustration only, and should not be construed as limiting the appended claims. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

EXAMPLES

Example 1 – Compositions of formulations

Table 1: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 50 mg core tablet, prepared according to the procedures of Example 2.1 and 2.2.

Component	Quality Reference	Function	Quantity per Unit (mg)
Granule composition:			
Binder Solution:			
HPMC 2910 15 mPa.s	Ph.Eur	Binder	22.50
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	5.60
Purified Water[a]	Ph.Eur	Solvent[a]	<750.00[a]>
Intragranular Phase:			
Abiraterone acetate	Company Specification	Active	500.00
Niraparib tosylate monohydrate[b]	Company Specification	Active	79.70[b]
Lactose monohydrate	Ph.Eur	Diluent	253.20
Crospovidone	Ph.Eur	Disintegrant	30.00
Extragranular Phase:			
Silicified Microcrystalline Cellulose	NF	Diluent	451.70
Crospovidone	Ph.Eur	Disintegrant	75.00
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	56.00
Colloidal Anhydrous Silica	Ph.Eur	Glidant	11.30
Magnesium Stearate	Ph.Eur	Lubricant	15.00
Core tablet weight:			1500.00

[a]Removed during processing

[b]Salt factor = 1.594; 79.70 mg niraparib tosylate is equivalent to 50.00 mg dose of niraparib (base)

Table 2: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 50 mg oral film coated tablet of Table 1, prepared according to the procedure of Example 2.3.

Component	Quality Reference	Function	Quantity per Unit (mg)
Abiraterone acetate: niraparib tosylate monohydrate 500 / eq. 50 mg oral tablet of Table 1			1500.00
Purified Water[a]	Ph.Eur	Processing Agent[a]	<240.00[a]>

Component	Quality Reference	Function	Quantity per Unit (mg)
Opadry® AMB II 88A620004 Yellow	Company Specification	Coating powder	60.00
Total Weight:			1560.00

[a]Removed during processing

Table 3: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 100 mg core tablet, prepared according to the procedures of Example 2.1 and 2.2

Component	Quality Reference	Function	Quantity per Unit (mg)
Granule composition:			
Binder Solution:			
HPMC 2910 15 mPa.s	Ph.Eur	Binder	24.00
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	5.60
Purified Water[a]	Ph.Eur	Solvent[a]	<800.00[a]>
Intragranular Phase:			
Abiraterone acetate	Company Specification	Active	500.00
Niraparib tosylate monohydrate[b]	Company Specification	Active	159.40[b].
Lactose monohydrate	Ph.Eur	Diluent	253.20
Crospovidone	Ph.Eur	Disintegrant	32.00
Extragranular Phase:			
Silicified Microcrystalline Cellulose	NF	Diluent	461.80
Crospovidone	Ph.Eur	Disintegrant	80.00
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	56.00
Colloidal Anhydrous Silica	Ph.Eur	Glidant	12.00
Magnesium Stearate	Ph.Eur	Lubricant	16.00
Core tablet weight:			1600.00

[a]Removed during processing
[b]Salt factor = 1.594; 159.40 mg niraparib tosylate is equivalent to 100.00 mg dose of niraparib (base)

Table 4: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 100 mg oral film coated tablet of Table 3, prepared according to the procedure of Example 2.3.

Component	Quality Reference	Function	Quantity per Unit (mg)
Abiraterone acetate: niraparib tosylate monohydrate 500 / eq. 100 mg oral tablet of Table 3			1600.00
Purified Water[a]	Ph.Eur	Processing Agent[a]	<256.00[a]>
Opadry® AMB II 88A170010 Beige	Company Specification	Coating powder	64.00
Total Weight:			1664.00

[a]Removed during processing

Table 5: Composition of abiraterone acetate: niraparib tosylate monohydrate, 333 / eq. 33 mg core tablet, prepared according to the procedures of Example 3.1, 3.2 and 3.3.

Component	Quality Reference	Function	Quantity per Unit (mg)
Internal Phase:			
Niraparib tosylate monohydrate[a]	Company Specification	Active	53.13[a]
Lactose monohydrate	Ph.Eur	Diluent	11.56
Microcrystalline Cellulose PH101	Ph.Eur	Diluent	37.25
Povidone K30	Ph.Eur	Binder	2.22
Crospovidone	Ph.Eur	Disintegrant	1.11
Colloidal Anhydrous Silica	Ph.Eur	Glidant	2.78
Magnesium Stearate	Ph.Eur	Lubricant	0.56
Abiraterone acetate granules[b]	Company Specification	Active	531.99
External Phase:			
Silicified Microcrystalline Cellulose (HD90)	NF	Diluent	533.30
Crospovidone	Ph.Eur	Disintegrant	65.50
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	37.30
Colloidal Anhydrous Silica	Ph.Eur	Glidant	10.00
Magnesium Stearate	Ph.Eur	Lubricant	13.30
Core tablet weight:			1300.00

[a]Salt factor = 1.594; 53.13 mg niraparib tosylate is equivalent to 33.00 mg dose of niraparib (base)

Table 6: Composition of abiraterone acetate: niraparib tosylate monohydrate, 333 / eq. 33 mg oral film coated tablet of Table 5, prepared according to the procedure of Example 3.4.

Component	Quality Reference	Function	Quantity per Unit (mg)
Abiraterone acetate: niraparib tosylate monohydrate 333 / eq. 33 mg oral tablet of Table 5			1300.00
Purified Water[a]	Ph.Eur	Processing Agent[a]	<221.00[a]>
Opadry® AMB II 88A220039 Yellow	Company Specification	Coating powder	39.00
Total Weight:			1339.00

[a]Removed during processing

Table 7: Composition of abiraterone acetate: niraparib tosylate monohydrate, 333 / eq. 67 mg core tablet, prepared according to the procedures of Example 3.1, 3.2 and 3.3.

Component	Quality Reference	Function	Quantity per Batch (kg)
Internal Phase:			
Niraparib tosylate monohydrate[a]	Company Specification	Active	1.063
Lactose monohydrate	Ph.Eur	Diluent	0.231
Microcrystalline Cellulose PH101	Ph.Eur	Diluent	0.745
Povidone K30	Ph.Eur	Binder	0.045
Crospovidone	Ph.Eur	Disintegrant	0.022
Colloidal Anhydrous Silica	Ph.Eur	Glidant	0.056
Magnesium Stearate	Ph.Eur	Lubricant	0.011
Abiraterone acetate granules	Company Specification	Active	5.320
External Phase:			
Silicified Microcrystalline Cellulose (HD90)	NF	Diluent	6.109
Crospovidone	Ph.Eur	Disintegrant	0.755
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	0.373
Colloidal Anhydrous Silica	Ph.Eur	Glidant	0.116
Magnesium Stearate	Ph.Eur	Lubricant	0.155
Core tablet weight:			15.001

[a]Salt factor = 1.594

Table 8: Composition of abiraterone acetate: niraparib tosylate monohydrate, 333 / eq. 67 mg oral film coated tablet of Table 7, prepared according to the procedure of Example 3.4.

Component	Quality Reference	Function	Quantity per Batch (kg) (11539 tablets)
Abiraterone acetate: niraparib tosylate monohydrate 333 / eq. 67 mg oral tablet of Table 7			15.00
Purified Water[a]	Ph.Eur	Processing Agent[a]	<2.55[a]>
Opadry® AMB II 88A220039 Yellow	Company Specification	Coating powder	0.45
Total Weight:			15.45

[a]Removed during processing

Table 9: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 100 mg core tablet prepared according to the procedures of Example 4.1 and 4.2.

Component	Quality Reference	Function	mg/tablet
Intragranular Phase:			
Abiraterone acetate	Company Specification	Active	500
Niraparib tosylate monohydrate[a]	Company Specification	Active	159.40
Lactose monohydrate	Ph.Eur	Diluent	110.0
Crospovidone	Ph.Eur	Disintegrant	40.0
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	5.6
Colloidal Anhydrous Silica	Ph.Eur	Glidant	8.0
Microcrystalline Cellulose PH101	NF	Diluent	349.00
Magnesium Stearate	Ph.Eur	Lubricant	4.0
Extragranular Phase:			
Silicified Microcrystalline Cellulose	NF	Diluent	308.0
Crospovidone	Ph.Eur	Disintegrant	40.0
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	56.0
Colloidal Anhydrous Silica	Ph.Eur	Glidant	8.0
Magnesium Stearate	Ph.Eur	Lubricant	12.0
Core tablet weight:			1600

[a]Salt factor = 1.594

Table 10: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 100 mg oral film coated tablet of Table 9 , prepared according to the procedure of Example 4.3.

Component	Quality Reference	Function	Quantity per Unit (mg)
Abiraterone acetate: niraparib tosylate monohydrate 500 / eq. 100 mg oral tablet of Table 5			1600.00
Purified Water[a]	Ph.Eur	Processing Agent[a]	<256.00[a]>
Opadry® AMB II 88A170010 Beige	Company Specification	Coating powder	64.00
Total Weight:			1664.00

[a]Removed during processing

Table 11: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 50 mg core tablet prepared according to the procedures of Example 4.1 and 4.2.

Component	Quality Reference	Function	mg/tablet
Intragranular Phase:			
Abiraterone acetate	Company Specification	Active	500
Niraparib tosylate monohydrate[a]	Company Specification	Active	79.70
Lactose monohydrate	Ph.Eur	Diluent	130.0
Crospovidone	Ph.Eur	Disintegrant	40.0
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	5.6
Colloidal Anhydrous Silica	Ph.Eur	Glidant	8.0
Microcrystalline Cellulose PH101	NF	Diluent	408.70
Magnesium Stearate	Ph.Eur	Lubricant	4.0
Extragranular Phase:			
Silicified Microcrystalline Cellulose	NF	Diluent	308.0
Crospovidone	Ph.Eur	Disintegrant	40.0
Sodium Lauryl Sulfate	Ph.Eur	Wetting agent	56.0
Colloidal Anhydrous Silica	Ph.Eur	Glidant	8.0
Magnesium Stearate	Ph.Eur	Lubricant	12.0
Core tablet weight:			1600

[a]Salt factor = 1.594

Table 12: Composition of abiraterone acetate: niraparib tosylate monohydrate, 500 / eq. 50 mg oral film coated tablet of Table 9 , prepared according to the procedure of Example 4.3.

Component	Quality Reference	Function	Quantity per Unit (mg)
Abiraterone acetate: niraparib tosylate monohydrate 500 / eq. 100 mg oral tablet of Table 5			1600.00
Purified Water[a]	Ph.Eur	Processing Agent[a]	<256.00[a]>
Opadry® AMB II 88A620004 Yellow	Company Specification	Coating powder	64.00
Total Weight:			1664.00

[a]Removed during processing

Example 2 – Preparation of a coated tablet comprising co-granules of abiraterone acetate and niraparib tosylate monohydrate, prepared by wet granulation

2.1 Wet granulation of abiraterone acetate and niraparib tosylate monohydrate

A binder solution was made by dissolving HPMC 2910 15 mPa.s and sodium lauryl sulfate in purified water until a clear solution was obtained. The ingredients abiraterone acetate, niraparib tosylate monohydrate, lactose monohydrate, and crospovidone were screened, pre-blended, and transferred into a suitable wet granulation equipment, the fluid bed granulator GPCG30. These ingredients were warmed up while fluidizing. The complete binder solution was sprayed upon

the ingredients using the wet granulation technique. The granulate was dried after spraying while fluidizing. The dried powder was collected and packed in aluminum bags.

Table 13: Granulometry Results for the granulate resulting from the granulation of the binder solution with the ingredients of the intragranular phase, of the composition of Table 1 and the composition of Table 3

Parameter	Table 1	Table 3
LOD (%)	1.46	1.41
Angle of repose (°)	34.73	35.07
Bulk density (g/mL)	0.403	0.397
Tapped density (g/mL)	0.455	0.431
d_{10}; d_{50}; d_{90} (µm)	230; 403; 726	256; 399; 695

The LOD profile for the granulates of the compositions of Table 1 and Table 3 is provided in Figure 6.

The sieve analysis is provided in Figure 7 for the granulate of Table 1 , and in Figure 8 for the granulate of Table 3 .

2.2 Extra-granular phase and compression

Silicified microcrystalline cellulose, crospovidone, sodium lauryl sulfate, and colloidal anhydrous silica were screened, and added to the fluid-bed granulate. All materials were screened and blended in a suitable blender. Magnesium stearate was screened and added to the container, and all materials were again blended in a suitable blender. The blend was then compressed into core tablets using the tablet press Module S (KC11).

The LOD, angle of repose, bulk density, and tapped density of the final blend of the compositions of Table 1 and Table 3 can be found in Table 14.

Table 14: LOD, Angle of Repose, and Densities of the Final Blend of the composition of Table 1 and the composition of Table 3

Parameter	Table 1	Table 3
LOD (%)	2.57	2.37
Angle of repose (°)	43.46	41.22
Bulk density (g/mL)	0.47	0.46
Tapped density (g/mL)	0.54	0.53

The blend uniformity (BU) results of the Final Blend of the composition of Table 1 and Table 3 are given in Table 15 and Table 16, while the stratified content uniformity results are presented in Table 17 and Table 18, respectively. The BU results indicate that both blends are well mixed and that both APIs are evenly distributed within the blend. The stratified content uniformity results demonstrate a good and evenly distribution of abiraterone acetate and niraparib tosylate monohydrate within the core tablets during the complete manufacturing

process. For the composition of Table 3 also the content uniformity is determined and can be found in Table 19.

Table 15: Blend Uniformity Results of the composition of Table 1

	Abiraterone acetate	Niraparib tosylate monohydrate
Mean	100.55	100.20
Minimum	97.19	96.88
Maximum	102.72	102.70

Table 16: Blend Uniformity Results of the composition of Table 3

	Abiraterone acetate	Niraparib tosylate monohydrate
Mean	99.70	100.22
Minimum	94.67	95.06
Maximum	103.42	103.84

Table 17: Stratified Content Uniformity Results of the composition of Table 1

	Abiraterone acetate	Niraparib tosylate monohydrate
Mean	102.61	102.17
Minimum	97.66	96.99
Maximum	109.76	108.35

Table 18: Stratified Content Uniformity Results of the composition of Table 3

Sample	Abiraterone acetate	Niraparib tosylate monohydrate	Tablet weight (g)
Mean	101.41	101.74	
Minimum	97.20	97.62	
Maximum	104.81	104.99	

Table 19: Content Uniformity Results of the composition of Table 3

	Abiraterone acetate	Niraparib tosylate monohydrate
Mean	101.32	102.18
Stdev	1.94	2.07
RSD	1.91	2.03

The resulting tablets were tested for weight, thickness, hardness, and disintegration time, and the results are shown in Table 20. The tablets were collected and packaged in a suitable container.

Table 20: Tablet Weight, Thickness, Hardness and Disintegration Time of the composition of Table 1 and the composition of Table 3

Composition reference	Sample	Average Weight (min-max) (mg, n = 10)	Average Thickness (min-max) (mm, n = 5)	Average Hardness (min-max) (N, n = 5)	Average Disintegration Time (min-max) (min:sec, n = 6)
Table 1	Sample 1	1504.4 (1500.2-1513.6)	7.81 (7.80-7.83)	267 (261-273)	02:59 (02:39-03:13)
	Sample 2	1506.6 (1502.7-1516.1)	7.83 (7.82-7.83)	273 (268-278)	03:06 (02:57-03:23)
	Sample 3	1502.7 (1496.8-1513.7)	7.81 (7.80-7.83)	266 (262-274)	02:51 (02:33-03:03)
	Sample 4	1503.9 (1496.8-1509.8)	7.81 (7.80-7.82)	268 (260-274)	03:07 (02:43-03:25)
	Sample 5	1505.5 (1496.5-1515.8)	7.80 (7.80-7.80)	265 (258-270)	03:12 (02:55-03:29)
Table 3	Sample 1	1608.1 (1597.0-1627.2)	8.06 (8.06-8.07)	330 (320-348)	03:07 (02:47-03:23)
	Sample 2	1601.7 (1585.3-1614.3)	8.05 (8.0-8.07)	321 (311-339)	03:02 (02:41-03:31)
	Sample 3	1595.2 (1579.4-1608.2)	8.06 (8.04-8.07)	306 (293-318)	03:36 (03:27-04:05)
	Sample 4	1597.5 (1580.6-1609.7)	8.04 (8.03-8.05)	316 (309-324)	04:27 (04:09-04:45)
	Sample 5	1597.9 (1583.8-1608.6)	8.04 (8.02-8.06)	316 (299-345)	03:39 (03:12-04:06)

All these results indicate that it was possible to successfully manufacture two clinical batches of abiraterone acetate/niraparib tosylate, i.e. the compositions of Tables 1 and 3.

2.3 Film coating

A coating suspension was prepared by dispersing coating powder in purified water until a suspension was obtained. The core tablets were transferred into a suitable coating pan. The coating solution was then sprayed upon the core tablets using the film coating technique. The film coated tablets were dried, after spraying, in the same coating pan. The coated tablets were collected and packaged in a suitable container.

The resulting film-coated tablets of Table 2 showed no scuffing and no other defects were observed.

The resulting film-coated tablets of Table 4 showed no scuffing defects and no white spots on their surface.

In summary, these film-coated tablets of Tables 2 and 4 were successfully manufactured without defects.

Example 3 – Preparation of a coated tablet comprising granules of abiraterone acetate prepared by fluid bed granulation, and niraparib tosylate monohydrate, the latter prepared by dry granulation

3.1 Dry granulation of niraparib tosylate monohydrate

Niraparib tosylate monohydrate, lactose monohydrate, microcrystalline cellulose, povidone K30, crospovidone, colloidal anhydrous silica, and magnesium stearate were screened and blended using a suitable blender. Following, the blend was milled and the milled material was further blended with a suitable blender. A dry granulate was made using a suitable compaction technique, e.g. a roller compacter, and the dry granulate was further milled using a suitable dry mill.

3.2 Wet granulation of abiraterone acetate

Abiraterone acetate, lactose monohydrate, and croscarmellose sodium were mixed and optionally sieved. A binder solution comprising hypromellose, sodium lauryl sulfate (SLS) and purified water, was prepared and added to the mixture of abiraterone acetate, lactose monohydrate, and croscarmellose sodium. Granules were then formed by fluid bed granulation and subsequently dried.

3.3 Extra-granular phase and compression

The obtained abiraterone acetate granules and niraparib tosylate monohydrate granules were screened and blended with silicified microcrystalline cellulose, crospovidone, sodium lauryl sulfate, and colloidal anhydrous silica, in a suitable blender. Magnesium stearate was screened and added to the container, and all materials were again blended in a suitable blender.

The blend containing niraparib tosylate monohydrate granules and abiraterone acetate granules was then compressed into core tablets using a suitable tablet press. The tablets were collected and packaged in a suitable container.

3.4 Film coating

A coating suspension was prepared by dispersing coating powder in purified water until a suspension was obtained. The core tablets were transferred into a suitable coating pan. The coating solution was then sprayed upon the core tablets using the film coating technique. The film coated tablets were dried, after spraying, in the same coating pan. The coated tablets were collected and packaged in a suitable container.

4.1 Dry granulation of niraparib tosylate monohydrate and abiraterone acetate

Abiraterone acetate, niraparib tosylate monohydrate, lactose monohydrate, crospovidone, sodium lauryl sulfate, colloidal anhydrous silica, microcrystalline cellulose, and magnesium stearate were screened and blended using a suitable blender. Following, the blend was milled

and the milled material was further blended with a suitable blender. A dry granulate was made using a suitable compaction technique, e.g. a roller compacter, and the dry granulate was further milled using a suitable dry mill.

4.2 Extra-granular phase and compression

The obtained abiraterone acetate and niraparib tosylate monohydrate co-granules were screened and blended with silicified microcrystalline cellulose, crospovidone, sodium lauryl sulfate, and colloidal anhydrous silica, in a suitable blender. Magnesium stearate was screened and added to the container, and all materials were again blended in a suitable blender.

The blend was then compressed into core tablets using a suitable tablet press. The tablets were collected and packaged in a suitable container.

4.3 Film coating

A coating suspension was prepared by dispersing coating powder in purified water until a suspension was obtained. The core tablets were transferred into a suitable coating pan. The coating solution was then sprayed upon the core tablets using the film coating technique. The film coated tablets were dried, after spraying, in the same coating pan. The coated tablets were collected and packaged in a suitable container.

Example 5 – Stability data of the prepared dried granules of Tables 1 and 3

After preparation of the dried granules of Tables 1 and 3, stability data show no degradation of abiraterone acetate and niraparib tosylate monohydrate. The oxidative degradants for abiraterone acetate remain within specification after 12 months at 5 ºC, 25 ºC/60%RH and 30 ºC/75%RH and after 6 months at 40 ºC/75%RH.

Example 6 – Dissolution method for testing in vitro release of active pharmaceutical ingredients of prepared compositions

The parameters of the dissolution methods are summarized in Table 21, below.

Table 21

Parameter	Value
Dissolution Apparatus:	Paddle (USP type 2, Ph.Eur, JP.)
Dissolution Medium Temperature:	37.0 ± 0.5 °C
Dissolution Medium Volume:	900 mL
Dissolution Medium:	0.25% (w/v) SLS in 0.05 M sodium phosphate buffer pH 4.5
Paddle Rotation Speed:	75 rpm

Parameter	Value
Sample Filter:	Syringe filter 0.2 µm pore size, regenerated cellulose membrane
Analytical Finish:	UHPLC with UV detection at 236 nm

USP= United States Pharmacopeia; JP= Japan; Ph.Eur.= European Pharmacopoeia; SLS= sodium lauryl sulfate; UHPLC= ultra high-performance liquid chromatography; UV= ultraviolet; w/v= weight/volume.

- *In vitro* dissolution curves for abiraterone acetate and niraparib are provided in Figures 5A and Figure 5B, respectively, for a combination of single agents being one capsule of 100-mg eq. niraparib, in its tosylate monohydrate form, and 2 tablets of 250-mg abiraterone acetate;
- a FDC tablet with the composition of Table 2 (50-mg eq. niraparib, in its tosylate monohydrate form, and 500-mg abiraterone acetate); and
- a FDC tablet with the composition of Table 4 (100-mg eq. niraparib, in its tosylate monohydrate form, and 500-mg abiraterone acetate).

Example 7 – A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic Prostate Cancer, MAGNITUDE

The primary objective of this study is to evaluate the effectiveness of niraparib and abiraterone acetate plus prednisone (AAP) compared to abiraterone acetate plus prednisone and placebo, as determined by radiographic progression-free survival (rPFS).

The study consists of 5 phases; a Prescreening Phase for biomarker evaluation only, a Screening Phase, a Treatment Phase, a Follow-up Phase, and an Extension Phase (either Open-label or Long-term, depending on Cohort assignment). A treatment cycle is defined as 28 days.

<u>Cohort 1: Subjects with mCRPC and HRR gene alteration</u>

Cohort 1 evaluates the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP) and HRR gene alteration. This cohort enrolls approximately 400 subjects.

<u>Cohort 2: Subjects with mCRPC and No HRR gene alteration</u>

Cohort 2 evaluates the combination of niraparib and AAP versus placebo and AAP in subjects with L1 mCRPC (ie, have not been treated with any therapy in the metastatic castrate-resistant setting, except for ADT and a limited exposure to AAP) and who have no HRR gene

alteration. The cohort may enroll approximately 600 subjects. A prespecified futility analysis was performed after approximately 200 subjects were enrolled and approximately 125 progression events had occurred in this cohort.

Cohort 3: Subjects with mCRPC receiving the FDC of niraparib and abiraterone acetate

To evaluate the clinical efficacy and safety of the FDC tablet formulation of niraparib and abiraterone acetate, a separate open-label cohort has been added to the study (Cohort 3). Up to approximately 100 subjects may be enrolled into Cohort 3 under the same inclusion/exclusion criteria and undergo the same study procedures as Cohort 1, except that subjects in Cohort 3 receive open-label niraparib+abiraterone acetate as an FDC tablet formulation instead of as single agents.

Study Populations

- Intent-to-Treat (ITT) Population: Randomized subjects from both Cohorts 1 and 2.
- Safety Population: Subjects in Cohorts 1 and 2 who receive at least one dose of study drug.
- FDC Population: Subjects in Cohort 3 who receive at least one dose of FDC.

Evaluations

- Efficacy evaluations include the following:
    - Radiographic progression-free survival (rPFS; primary endpoint): evaluated by tumor measurements using CT or MRI scans and whole-body bone scans (^{99m}Tc). Scans are collected and reviewed by a central vendor.
    - Serum prostate-specific antigen (measurements at a central laboratory) evaluated by Prostate Cancer Working Group 3 (PCWG3) criteria.
    - Survival status.
    - Subsequent systemic therapy for prostate cancer.
    - Cancer-related radiation therapy or surgical procedures.
    - Symptomatic progression.
    - Patient-reported outcomes.
- PK evaluations. Blood samples to measure plasma levels of niraparib and its metabolite, (if judged relevant), are obtained on Day 1 of Cycles 2 through 7. Population PK parameters and derived exposure are also determined for niraparib. Blood samples to measure plasma levels of abiraterone are obtained pre-dose on Day 1 of Cycles 2 and 3.
- Biomarker evaluations: HRR gene alteration status is evaluated from blood and tumor tissue (archival or recently collected) samples. Other exploratory biomarker analyses are also performed where allowed by local regulations.
- Safety evaluations: Safety assessments are based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, clinical safety

laboratory tests, Eastern Cooperative Oncology Group Performance Score, ECG, and other safety evaluations at specified timepoints.

Prescreening Eligibility Criteria

1. Signed informed consent form (ICF).
2. ≥18 years of age (or the local legal age of consent)
3. Histologically confirmed prostate cancer.
4. Can provide a blood sample for determination of HRR gene alterations.
5. Willing to provide a tumor tissue sample (archival or recently collected) for determination of HRR gene alterations selected from BRCA1, BRCA2, CDK12, FANCA, PALB2, CHEK2, BRIP1, HDAC2, and ATM.
6. Metastatic prostate cancer in the setting of castrate levels of testosterone (ie, taking a gonadotropin releasing hormone analog [GnRHa], or history of bilateral orchiectomy at study entry).

Inclusion Criteria

1. HRR gene alteration status as follows:
    a. Cohort 1: positive for HRR gene alteration
    b. Cohort 2: not positive for HRR gene alteration (ie, no HRR gene alteration)
    c. Cohort 3: positive for HRR gene alteration and receiving FDC
2. Metastatic disease documented by positive bone scan or metastatic lesions on computed tomography (CT) or magnetic resonance imaging (MRI).
3. Metastatic prostate cancer in the setting of castrate levels of testosterone ≤50 ng/dL on a GnRHa or bilateral orchiectomy as evidenced by prostate-specific antigen (PSA) progression or radiographic progression.
4. Able to continue GnRHa during the study if not surgically castrate.
5. Eastern Cooperative Oncology Group Performance Score (ECOG PS) Grade of 0 or 1
6. Score of ≤3 on the Brief Pain Inventory-Short Form (BPI-SF) Question #3 (worst pain in last 24 hours).
7. Clinical laboratory values at Screening:
    a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L.
    b. Hemoglobin ≥9.0 g/dL, independent of transfusions for at least 30 days.
    c. Platelet count ≥100 x 10^9/L.
    d. Serum albumin ≥3.0 g/dL.

e. Creatinine clearance ≥30 mL/min either calculated or directly measured via 24-hour urine collection.

f. Serum potassium ≥3.5 mmol/L.

g. Serum total bilirubin ≤1.5 x upper limit of normal (ULN) or direct bilirubin ≤1 x ULN (Note: in subjects with Gilbert's syndrome, if total bilirubin is >1.5 x ULN, measure direct and indirect bilirubin, and if direct bilirubin is ≤1.5 x ULN, subject may be eligible as determined by the medical monitor).

h. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x ULN.

8. Able to swallow the study drug tablets and capsules whole.
9. While on study drug and for 3 months following the last dose of study drug, a male subject must agree to use an adequate contraception method as deemed appropriate by the investigator and agree not to donate sperm.
10. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion Criteria

1. Prior treatment with a PARP inhibitor.
2. Systemic therapy (ie, novel second-generation AR-targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy, or more than 4 months of AAP prior to randomization) in the mCRPC setting; or AAP outside of the mCRPC setting.
3. For subjects who received 2 to 4 months of AAP prior to randomization for the treatment of mCRPC, evidence of progression by PSA (per PCWG3) during screening. These potential subjects are required to have 2 PSA values during the Prescreening and Screening Phases. The second PSA value should be within 2 weeks of randomization. If PSA rise is thought to be due to flare, the investigator should confirm that there is no radiographic progression.
4. Symptomatic brain metastases.
5. History or current diagnosis of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).
6. Other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤2 years prior to randomization, or malignancy that currently requires active systemic therapy.
7. Severe or unstable angina, myocardial infarction or ischemia requiring coronary artery bypass graft or stent within the previous 6 months, symptomatic congestive heart failure, arterial or venous thromboembolic events (eg, pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular

arrhythmias within 6 months prior to randomization or New York Heart Association (NYHA) Class II to IV heart disease.

8. Presence of uncontrolled hypertension (persistent systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension are allowed, if BP is controlled to within these limits by anti-hypertensive treatment.
9. Current evidence of any of the following:

    a. Any medical condition that would make prednisone use contraindicated.

    b. Any chronic medical condition requiring a higher dose of corticosteroid than 10 mg prednisone (or equivalent) once daily.

10. Active or symptomatic viral hepatitis or chronic liver disease (as evidenced by ascites, encephalopathy, or bleeding disorders secondary to hepatic dysfunction).
11. History of adrenal dysfunction
12. Known allergies, hypersensitivity, or intolerance to AA or niraparib or the corresponding excipients.
13. Subjects who are receiving opioid analgesics at the time of screening.
14. Human immunodeficiency virus (HIV) positive subjects with 1 or more of the following:

    a. Not receiving highly active antiretroviral therapy.

    b. Receiving antiretroviral therapy that may interfere with the study drug.

    c. A change in antiretroviral therapy within 6 months of the start of screening (except if a change is made to avoid a potential drug-drug interaction with the study drug).

    d. CD4 count <350 at screening.

    e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening.

15. Subjects who have had the following ≤28 days prior to randomization:

    a. A transfusion (platelets or red blood cells).

    b. Hematopoietic growth factors.

    c. An investigational agent for prostate cancer.

    d. Major surgery (sponsor should be consulted regarding what constitutes major surgery).

    e. Radiation therapy.

Example 8 – A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and

Prednisone for the Treatment of Participants with Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Mutated Metastatic Castration-Sensitive Prostate Cancer (mCSPC), AMPLITUDE

The objectives of this study are:

- to determine if niraparib and abiraterone acetate, plus prednisone compared with abiraterone acetate plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC provides superior efficacy in improving radiographic progression-free survival (rPFS);
- to assess the clinical benefit of niraparib and abiraterone acetate, plus prednisone compared with abiraterone acetate plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC;

to characterize the safety profile of niraparib and abiraterone acetate, plus prednisone compared with abiraterone acetate plus prednisone in participants with deleterious germline or somatic HRR gene-mutated mCSPC.

Approximately 788 participants are randomly assigned in a 1:1 ratio to either niraparib 200 mg, and abiraterone acetate 1000 mg, plus prednisone 5 mg daily; or abiraterone acetate 1000 mg plus prednisone 5 mg daily. All participants must be receiving background androgen deprivation therapy (ADT; ie, gonadotropin-releasing hormone analogue or surgical castration). The study consists of 4 phases: a Prescreening Phase for biomarker evaluation for eligibility only, a Screening Phase, a Treatment Phase, and a Follow-up Phase.

Inclusion Criteria

1. Each potential participant must satisfy all of the following criteria to be enrolled in the study:
2. >18 years of age (or the local legal age of consent).
3. Diagnosis of prostate adenocarcinoma.
4. Metastatic disease documented by ≥1 bone lesion(s) on ^{99m}Tc bone scan. Participants with
5. a single bone lesion must have confirmation of bone metastasis by CT or MRI.
6. Must have at least one of the deleterious germline or somatic HRR gene alterations selected from BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, PALB2, RAD51B, and RAD54L.
7. Eastern Cooperative Oncology Group Performance Status (ECOG PS) Grade <2.
8. Androgen deprivation therapy (either medical or surgical castration) must have been started >14 days prior to randomization and willing to continue through the treatment phase. Participants who start a GnRH agonist <28 days prior to randomization are required to take a first-generation anti-androgen for >14 days prior to randomization. The anti-androgen must be discontinued prior to randomization.

9. Participants who have received prior docetaxel treatment must meet the following criteria:

    a. Received a maximum of 6 cycles of docetaxel therapy for mCSPC

    b. Received the last dose of docetaxel <2 months prior to randomization

    c. Maintained a response to docetaxel of stable disease or better, by investigator assessment of imaging or PSA, prior to randomization.

10. Other allowed prior therapy for mCSPC:

    a. Maximum of 1 course of radiation or surgical intervention to manage symptoms of prostate cancer. Radiation with curative intent is not allowed. Radiation must be completed prior to randomization.

    b. <6 months of ADT prior to randomization.

    c. 30 days of abiraterone acetate plus prednisone allowed if required.

11. Allowed prior treatments for localized prostate cancer (all treatments must have been completed ≥1 year prior to randomization):

    a. ≤3 years total of ADT

    b. All other forms of prior therapies including radiation therapy, prostatectomy, lymph node dissection, and systemic therapies.

12. Clinical laboratory values at Screening:

    a. Absolute neutrophil count ≥1.5 x 10^9/L

    b. Hemoglobin ≥9.0 g/dL, independent of transfusions for at least 28 days

    c. Platelet count ≥100 x 10^9/L

    d. Creatinine <2 x upper limit of normal (ULN)

    e. Serum potassium ≥3.5 mmol/L

    f. Serum total bilirubin ≤1.5× ULN or direct bilirubin ≤1 x ULN (Note: In participants with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin, and if direct bilirubin is ≤1.5 × ULN, participant may be eligible)

    g. AST or ALT ≤3 × ULN

13. Able to swallow the study medication tablets whole.
14. Must sign informed consent (written or remote/virtual) indicating that he understands the purpose of, and procedures required for, the study and is willing to participate in the study including providing a DNA sample.

15. While on study medication and for 3 months following the last dose of study medication, a male participant must agree to use an adequate contraception method as deemed appropriate by the investigator.
16. A male participant must agree not to donate sperm while on study treatment and for a minimum of 3 months following the last dose of study medication.

Exclusion Criteria

Any potential participant who meets any of the following criteria is excluded from participating in the study:

1. Pathological finding consistent with small cell ductal or neuroendocrine carcinoma of the prostate.
2. Prior treatment with a PARP inhibitor.
3. Prior AR-targeted therapy (eg, ketoconazole for prostate cancer, apalutamide, enzalutamide, darolutamide), immunotherapy, or radiopharmaceutical agents with the exception of only 30 days of abiraterone acetate plus prednisone allowed prior to randomization.
4. Initiation of treatment with a bisphosphonate or denosumab for the management of bone metastasis <28 days prior to randomization.
5. History of adrenal dysfunction
6. Long-term use of systemically administered corticosteroids (>5 mg of prednisone or the equivalent) during the study is not allowed. Short-term use (≤4 weeks, including taper) and locally administered steroids (eg, inhaled, topical, ophthalmic, and intra-articular) are allowed, if clinically indicated.
7. Active malignancies (ie, progressing or requiring treatment change in the last 24 months) other than the disease being treated under study. The only allowed exceptions are:

    a. non-muscle invasive bladder cancer;

    b. skin cancer (non-melanoma or melanoma) treated within the last 24 months that is considered completely cured;

    c. breast cancer – adequately treated lobular carcinoma in situ or ductal carcinoma in situ;

    d. malignancy that is considered cured with minimal risk of recurrence.

8. History or current diagnosis of MDS/AML.
9. Current evidence within 6 months prior to randomization of any of the following: severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, clinically significant arterial or venous thromboembolic events (eg, pulmonary embolism), or clinically significant ventricular arrhythmias.

10. Presence of sustained uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg). Participants with a history of hypertension are allowed, provided that blood pressure is controlled to within these limits by an antihypertensive treatment.
11. Known allergies, hypersensitivity, or intolerance to the excipients of niraparib, abiraterone acetate, or niraparib/abiraterone acetate FDC.
12. Current evidence of any medical condition that would make prednisone use contraindicated.
13. Received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study medication.
14. Participants who have had the following ≤28 days prior to randomization:

    a. A transfusion (platelets or red blood cells);

    b. Hematopoietic growth factors;

    c. Major surgery (sponsor should be consulted regarding what constitutes major surgery).

15. Human immunodeficiency virus positive participants with 1 or more of the following:

    a. Not receiving highly active antiretroviral therapy or on antiretroviral therapy for less than 4 weeks.

    b. Receiving antiretroviral therapy that may interfere with the study medication (consult the sponsor for review of medication prior to enrollment).

    c. A change in antiretroviral therapy within 6 months of the start of screening (except if, after consultation with the sponsor on exclusion criterion, a change is made to avoid a potential drug-drug interaction with the study medication).

    d. CD4 count <350 at screening.

    e. An acquired immunodeficiency syndrome-defining opportunistic infection within 6 months of the start of screening.

    f. Human immunodeficiency virus load >400 copies/mL.

16. Active or symptomatic viral hepatitis or chronic liver disease; encephalopathy, ascites or bleeding disorders secondary to hepatic dysfunction.
17. Severe hepatic impairment Class C per Child-Pugh classification system.