(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

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 disclosure 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 disclosure 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 disclosure is to provide pharmaceutical formulations that support patient compliance, therapy adherence, and therapy efficiency.

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

An objective of the present disclosure 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 examples, the abiraterone acetate and niraparib tosylate monohydrate are homogeneously distributed within an intragranular phase. In some examples, the abiraterone acetate and niraparib tosylate monohydrate are homogenously distributed within the dosage form, e.g., tablet. In some examples, 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 disclosure. 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 disclosure is to provide granules comprising abiraterone acetate and niraparib tosylate monohydrate with a good stratified content uniformity.

An objective of the present disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 disclosure 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 example, the mCRPC treatment is first-line (L1) treatment of mCRPC. In one aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone in treating prostate cancer, optionally wherein the prostate cancer is mCRPC, optionally wherein the mCRPC is first-line (L1) mCRPC, in a male human patient. In an example, the patient has not been treated with abiraterone acetate plus prednisone for more than 5 months. In an example, the patient is positive for homologous recombination deficiency (HRD), or the patient is not positive for HRD. In an example, 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 example, 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 example, 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 example, 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 example, the patient has

undergone ADT prior to the treatment with the pharmaceutical formulation, plus prednisone. In an example, said ADT is a medical or surgical castration. In an example, said ADT started within 6 months, preferably at least 14 days, prior to the treatment with the pharmaceutical formulation, plus prednisone. In an example, the patient undergoes ADT during the treatment with the pharmaceutical formulation, plus prednisone. In an example, 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 example, the patient has received docetaxel or cabazitaxel prior to the treatment with the pharmaceutical formulation, plus prednisone. In an example, the patient has received radiation or surgical intervention, prior to the treatment with the pharmaceutical formulation, plus prednisone. In an example, the patient has received abiraterone acetate plus prednisone, prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient has received abiraterone acetate plus prednisone, during a month prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient has received treatments for localized prostate cancer, prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, 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 example, 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 another aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating mCRPC, with or without DNA-repair gene defects (DRD) or HRD, and optionally with cyclin dependent kinase 12 (CDK12) pathogenic alterations, in a male human patient. In an example, the patient continues with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated. In an example, 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 example, 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 another aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the

manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone and leuprorelin acetate, in treating high risk and lymph node positive prostate cancer, prior to, during, and after radiotherapy, in a male human patient. In an example, 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 another aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating castration-naïve prostate cancer, with or without metastases, in a male human patient. In an example, 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 example, 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 example, the patient is HRD biomarker positive, high risk, and/or with oligometastatic disease. In an example, 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. In another aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating locally advanced prostate cancer in a male human patient who is candidate for primary radiotherapy.

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. In another aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating mCRPC in a male human patient optionally having received prior chemotherapy comprising docetaxel or cabazitaxel.

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 another aspect, the present disclosure relates to use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating non-metastatic CRPC (nmCRPC) in a male human patient. In an example, the patient has a PSA doubling time equal to or less than 10 months and is HRD positive. In an example, the patient is HRD positive. In an example, 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 example, 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 example, the FrDC or FDC are oral dosage forms. In an example, 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 example, the patient has not been treated with abiraterone acetate and prednisone for more than 5 months. In an example, the patient is positive for homologous recombination deficiency (HRD), or the patient is not positive for HRD. In an example, 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 example, 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 example, 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 example, 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 example, the patient has undergone ADT prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, said ADT is medical or surgical castration. In an example, said ADT started within 6 months, preferably at least 14 days, prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient undergoes ADT during the treatment with the pharmaceutical formulation plus prednisone. In an example, 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 example, the patient has received

docetaxel or cabazitaxel prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient has received radiation or surgical intervention, prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient has received abiraterone acetate plus prednisone, prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient has received abiraterone acetate plus prednisone, during a month prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, the patient has received treatments for localized prostate cancer, prior to the treatment with the pharmaceutical formulation plus prednisone. In an example, 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 example, 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 example, the patient continues with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated. In an example, 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 example, 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 example, 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 example, 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 example, said biochemical recurrent prostate cancer is detected by: i) a prostate-specific antigen (PSA) rise of ≥ 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 example, the patients are HRD biomarker positive, high risk, and/or with oligometastatic disease. In an example, 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 example, the patients have a PSA doubling time equal to or less than 10 months and are HRD positive. In an example, the patients are HRD positive. In an example, 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 example, 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 example, the FrDC or FDC are oral dosage forms. In an example, 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 example, the granules consist essentially of abiraterone acetate, niraparib, and a pharmaceutically acceptable carrier. In an example, 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 example, 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 example, 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 example, the niraparib tosylate monohydrate is in crystal form. In an example, the abiraterone acetate is in crystal form. In an example, the present disclosure relates to a pharmaceutical formulation comprising niraparib lauryl sulfate and a pharmaceutically acceptable carrier. In an example, 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 example, 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 example, the diluent is lactose, and said lactose is also used as a binder. In an example, 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 example, 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 example, 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 example, 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 example, 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 example, the SLS is present both in the intragranular and extragranular phases of the tablet. In an example, the disintegrant is crospovidone and is present both in the intragranular and extragranular phases of the tablet. In as example, the diluent of the extragranular phase is silicified microcrystalline cellulose. In an example, the tablet has a hardness of 250 to 350 N. In an example, the tablet has a stratified content uniformity from 75% to 125%, or from 90% to 110%. In an example, the tablet has a blend uniformity with a relative standard deviation up to 3%.

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

In an example, 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 example, 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 example, the patient has first-line (L1) mCRPC and is positive for DRD or HRD. In an example, the patient has deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCSPC. In an example, 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 example, the patient has high-risk localized prostate cancer.

In an example, the patient is in a risk group selected from very low, low, intermediate favorable, intermediate unfavorable, high, very high, and regional. In an example, 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 example, 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 example, the medical use or method of treatment comprises administering 1, 2, or 3 oral dosage forms per day. In an example, 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 example, 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 example, the binder solution comprises a binder, the wetting agent and a solvent. In an example, the inlet air temperature during the wet granulating of step (c), is from 25 °C to 65 °C. In an example, the spray rate during the wet granulating of step (c), is from 190 to 300 g/min. In an example, 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 example, the obtained granule composition is further compressed into a tablet optionally with a lubricant. In an example, the process further comprises preparing a coating suspension and coating the tablet with said suspension.

In an example, 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

CLAIMS

1. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone in treating prostate cancer, optionally wherein the prostate cancer is mCRPC, optionally wherein the mCRPC is first-line (L1) mCRPC, in a male human patient.
2. The use of claim 1, wherein the patient is positive for homologous recombination deficiency (HRD), or the patient is not positive for HRD.
3. The use of claim 2, wherein 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).
4. The use of any one of claims 1-3, wherein the patient had received gonadotropin releasing hormone agonists (GnRHa) therapy or had undergone bilateral orchiectomy, prior to the treatment with the pharmaceutical formulation plus prednisone.
5. The use of any one of claims 1-4, wherein the patient is to continue with GnRHa therapy during the treatment with the pharmaceutical formulation, plus prednisone, if not surgically castrated.
6. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating mCRPC, with or without DNA-repair gene defects (DRD) or HRD, and optionally with cyclin dependent kinase 12 (CDK12) pathogenic alterations, in a male human patient.
7. The use of claim 6, wherein the patient is to continue with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated.
8. The use of claim 6, wherein the patient had 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.
9. The use of claim 8, wherein said anti-androgens are washed-out prior to the treatment with the pharmaceutical formulation plus prednisone.
10. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone and leuprorelin acetate, in treating high risk and lymph node positive prostate cancer, prior to, during, and after radiotherapy, in a male human patient.

11. The use of claim 10, wherein said radiotherapy is stereotactic body radiotherapy (SBRT) or ultra-hypofractionated radiotherapy, with a total dose of about 37.5 to 40 Gy.
12. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating castration-naïve prostate cancer, with or without metastases, in a male human patient.
13. The use of claim 12, wherein the patient is to continue with GnRHa therapy during the treatment with the pharmaceutical formulation plus prednisone, if not surgically castrated.
14. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating biochemical recurrent prostate cancer, in a male human patient.
15. The use of claim 14, wherein 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).
16. The use of claim 14 or 15, wherein the patients are HRD biomarker positive, high risk, and/or with oligometastatic disease.
17. The use of claim 16, wherein 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.
18. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating locally advanced prostate cancer in a male human patient who is candidate for primary radiotherapy.
19. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating mCRPC in a male human patient optionally having received prior chemotherapy comprising docetaxel or cabazitaxel.
20. Use of a pharmaceutical formulation comprising abiraterone acetate and niraparib tosylate monohydrate in the manufacture of a combined preparation for simultaneous, separate or sequential use with prednisone, in treating non-metastatic CRPC (nmCRPC) in a male human patient.
21. The use of claim 20, wherein the patients have a PSA doubling time equal to or less than 10 months and are HRD positive.
22. The use of claim 20, wherein the patients are HRD positive.
23. The use of claim 20, wherein the patients have high-risk BCR.

24. The use of any one of claims 1-23, wherein said pharmaceutical formulation comprises a free-dose combination (FrDC) of abiraterone acetate and niraparib; or a FrDC of abiraterone acetate and niraparib tosylate monohydrate.
25. The use of any one of claims 1-23, wherein said pharmaceutical formulation comprises a fixed-dose combination (FDC) comprising abiraterone acetate and niraparib; or a FDC comprising abiraterone acetate and niraparib tosylate monohydrate.
26. The use of claim 24 or claim 25, wherein 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.
27. The use of any one of claims 24-26, wherein the FrDC or FDC are oral dosage forms.
28. The use of claim 27, wherein the oral dosage form is a tablet, a capsule, or a sachet.
29. The use of any one of claims 1-23, wherein said pharmaceutical formulation comprises a fixed-dose combination (FDC) as defined in any one of Tables 1-12.