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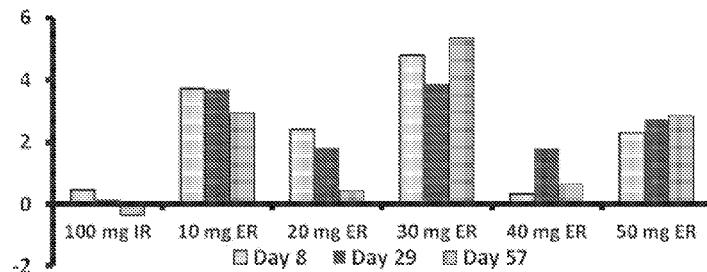
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Figure 3



(57) Abstract: Onapristone extended-release formulations and methods of administering onapristone extended-release formulations are provided. Onapristone extended-release formulations provide sufficient therapeutic activity as compared to immediate-release formulations with reduced potential for adverse side effects. Aspects described herein provide extended-release pharmaceutical compositions comprising onapristone as the active ingredient in an amount from about 2 mg to about 100 mg. The extended-release pharmaceutical compositions (also referred to herein as ER formulations) further comprise excipients suitable for the desired dosage form (e.g., tablet, capsule, etc.) and for delaying the release of the active ingredient.

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ONAPRISTONE EXTENDED-RELEASE COMPOSITIONS AND METHODS

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 62/080,868, filed November 17, 2014. The above referenced application is incorporated herein by reference as if restated in full. The above referenced application and all references cited herein, including but not limited to patents and patent applications, are incorporated by reference in their entirety.

BACKGROUND

[0002] Onapristone (ONA) is an anti-progestin drug and progesterone receptor antagonist which was originally developed for potential contraceptive use and the use in benign gynecological disorders such as the treatment of uterine leiomyomas. However, onapristone has demonstrated substantial activity in advanced breast cancer. It is thought that ONA binds to the progesterone receptor (PR), preventing the PR from binding to DNA and thereby inhibiting or eliminating PR-induced DNA transcription. See, e.g., Klijn et al., Progesterone antagonists and progesterone receptor modulation in the treatment of breast cancer, *Steroids*, v. 65, pp. 825-830 (2000); Jonat et al., The clinical efficacy of progesterone antagonists in breast cancer, *Endocrine Therapy of Breast Cancer*, pp. 117-124.

[0003] Onapristone is a type I progesterone receptor (PR) antagonist, which prevents PR-induced DNA transcription. Presence of transcriptionally activated PR (APR) in tissue samples from a cancer patient, measured using, for example, an immunohistochemistry companion diagnostic procedure, indicates susceptibility to treatment with onapristone anticancer activity.. Onapristone anti-cancer activity is documented in multiple pre-clinical models and clinical studies in patients with hormone therapy-naive or tamoxifen-resistant breast cancer. Despite promising activity in breast cancer models, the development of onapristone as an oncology drug was terminated due to liver function test abnormalities. See, e.g., Robertson et al., *Eur J Cancer*. 35(2):214-8 (Feb. 1999).

[0004] Expression of the progesterone receptor (PR) has been described in breast [Mote 2000, Lange 2008], endometrial [Kim 2013, Mortel 1984], prostate [Lange 2007, Bonkhoff 2001], ovarian [Sieh 2013], and several other cancers [Yin 2010, Ishibashi 2005, Blankenstein 2000]. Antiprogestins have been shown to have an inhibitory effect on the growth of different type of cancer cells, and antiprogestin treatment has been studied in breast [Jonat 2013], endometrial [Thigpen 1999], prostate [Taplin 2008] cancers and uterine sarcomas [Koivisto-Korander 2007].

[0005] The effects of progesterone are mediated by two distinct nuclear receptor proteins, PRA and PRB, two transcriptional isoforms of the single PR gene. In luminal epithelial cells of the normal breast and in normal endometrium, both PR isoforms are expressed and are required to mediate the physiological effects of progestin ligands [Mote 2002, Arnett-Mansfield 2004]. The two PR isoforms have both been detected in malignant tissues, such as breast, endometrial, ovarian and prostate cancers [Cottu 2015].

[0006] ONA is a type I antiprogestin which prevents PR monomers from dimerizing, inhibits ligand-induced phosphorylation, prevents association of the PR with its co-activators, and thus prevents PR-mediated DNA transcription. ONA does not allow the PR complex to bind to DNA, does not or minimally modulates PR-mediated genes, and inhibits ligand-induced PR phosphorylation, in contrast to other antiprogestins [Beck 1996; Afhüppe 2009]. Preclinical activity has been shown in several models, including endometrial cancer [Mueller 2003] and the clinical anticancer activity of ONA has been previously documented in patients with hormone therapy-naïve [Robertson 1999] or tamoxifen-resistant [Jonat 2002] breast cancer.

[0007] Transcriptionally activated PR (APR) can be detected by observational evaluation of the subnuclear distribution pattern using immunohistochemistry (IHC). Using this method, APR can be used as a potentially predictive IHC biomarker in endometrioid cancer of the uterus. See, U.S. Patent Number 9,046,534. APR detection is being developed as a companion diagnostic to identify patients more likely to respond to ONA [Bonneterre 2015].

[0008] Early clinical studies employing the original immediate release (IR) formulation of ONA have shown that ONA is well-tolerated with the exception of abnormalities in liver

function tests (LFTs) [Cameron 1996, Cameron 2003, Croxatto 1994, Jonat 2002, Robertson 1999]. Studies with the original IR formulation were discontinued due to these LFT abnormalities. Id.

[0009] Previously, onapristone was provided to patients with cancer (e.g., breast, endometrial, others) in an immediate release formulation of 100 mg and provided QD (once per day). Onapristone has also been given to patients in endocrinology studies, at immediate release doses of 1 and 10 mg doses resulting in a dose-dependent effect of onapristone on suppression of gonadotrophin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion. Cameron 2003. However, these studies used immediate release formulations of onapristone of unknown purity. Importantly, these studies addressed the dose and formulation of onapristone suitable for potential contraceptive use rather than the dose and formulation suitable for treating a disease such as cancer.

[0010] What is needed is an improved formulation of onapristone which allow for a continuous suppression of the PR and methods of administering the same resulting in sufficient bioavailability to provide clinical benefit to cancer patients at doses which result in less toxicity than the previous clinical experience with onapristone.

SUMMARY

[0011] Aspects described herein provide extended-release pharmaceutical compositions comprising onapristone as the active ingredient in an amount from about 2 mg to about 100 mg. The extended-release pharmaceutical compositions (also referred to herein as ER formulations) further comprise excipients suitable for the desired dosage form (e.g., tablet, capsule, etc.) and for delaying the release of the active ingredient.

[0011a] In one aspect, there is provided extended release pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg to about 50 mg.

[0012] Further aspects provide onapristone ER formulations utilizing highly purified onapristone (e.g., at least about 98%). In another aspect, the ratio of onapristone to inactive excipients in the ER formulations is about 0.05 to about 5%.

[0013] In a further aspect, the AUC (area under the curve) of onapristone is at least about 1578 ng*h/ml over about an 8-12 hour period after administration of a 10 mg dose BID (i.e., twice per day) to a patient.

[0014] In another aspect, the Cmax (maximum plasma concentration) of onapristone is at least about 240 ng/ml over about an 8-12 hour period after administration of a 10 mg dose BID to a patient. In yet another aspect, a steady state plasma concentration of onapristone is achieved at about 8 days following the initial dose of the extended release onapristone pharmaceutical composition. In another aspect, the extended-release onapristone pharmaceutical composition comprises at least about 10 mg to about 50 mg of onapristone.

[0014a] In another aspect, there is provided a method of administering onapristone to a patient having cancer comprising administering an extended release onapristone pharmaceutical composition twice per day to the patient, wherein the extended release onapristone pharmaceutical composition comprises of at least about 2 mg to about 50 mg of onapristone.

[0014b] In yet another aspect, there is provided a method of treating a human subject having a disorder capable of treatment with onapristone comprising administering the extended release onapristone pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg to about 50 mg to the human subject twice per day, wherein the AUC of onapristone following the administration of 10 mg of the extended release formulation to a patient twice per day is at least about 1578 ng*h/ml over about 8-12 hours.

[0014c] In another aspect, there is provided a method of treating a human subject having a disorder capable of treatment with onapristone comprising administering to said subject 10 mg of the extended release onapristone pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg

to about 50 mg twice per day, wherein the Cmax of onapristone in the human subject is at least about 240 ng/ml over about 8-12 hours.

[0014d] In another aspect, there is provided a method of treating a human subject having a disorder capable of treatment with onapristone comprising administering to said subject the extended release pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg to about 50 mg twice per day, wherein a steady state plasma concentration is achieved at about 8 days.

[0014e] In another aspect, there is provided a method of administering onapristone to a patient having a cancer comprising administering an extended-release onapristone pharmaceutical composition to the patient, wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate.

[0014f] In another aspect, there is provided a method of treating a human subject having a cancer which expresses the progesterone receptor comprising administering an extended-release onapristone pharmaceutical composition to the human subject wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate, and wherein the AUC of onapristone following the administration of the extended-release onapristone pharmaceutical composition is at least about 1578 ng*h/ml over about 8-12 hours.

[0014g] In another aspect, there is provided a method of treating a human subject having a cancer which expresses the progesterone receptor comprising administering an extended-release onapristone pharmaceutical composition wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5%

magnesium stearate, and wherein the Cmax of onapristone following the administration of the extended-release onapristone pharmaceutical composition in the human subject is at least about 240 ng/ml over about 8-12 hours.

[0014h] In another aspect, there is provided a method of treating a human subject having a cancer which expresses the progesterone receptor comprising administering an extended-release pharmaceutical composition wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate, and wherein a steady-state plasma concentration of onapristone following the administration of the extended-release onapristone pharmaceutical composition in the human subject is achieved at about 8 days.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 shows the exemplary Cmax (maximum active ingredient concentration) levels per ONA dose level (10 mg, 20 mg, 30 mg, 40 mg, 50 mg extended-release BID (twice per day) and 100 mg QD (once per day));

[0016] Figure 2 shows the exemplary AUC (area under the curve) per ONA dose level (10 mg, 20 mg, 30 mg, 40 mg, 50 mg extended-release formulations BID (twice per day) and 100 mg QD (once per day));

[0017] Figure 3 shows the exemplary accumulation of ONA over time per ONA dose level (10 mg, 20 mg, 30 mg, 40 mg, 50 mg extended-release formulations BID (twice per day) and 100 mg QD (once per day)); and

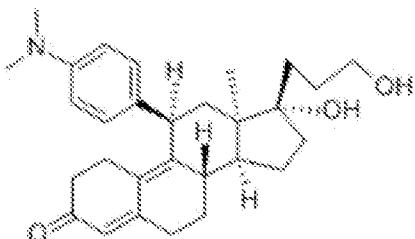
[0018] Figures 4A and 4B show exemplary ONA plasma levels over time per dose levels for the extended-release formulations BID (Figure 4A) and the 100 mg formulation QD.

DETAILED DESCRIPTION

[0019] Before describing several exemplary aspects described herein, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The aspects described herein are capable of being practiced or being carried out in various ways.

[0020] In another aspect onapristone ER formulations comprise onapristone (ONA) ((8S,11R,13R,14S,17S)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(3-hydroxypropyl)-13-methyl-1,2,6,7,8,11,12,14,15,16-deahydrocyclopenta[a]phenanthren-3-one), an anti-progestin drug and progesterone receptor antagonist having the following structure:

[Text continued on page 5]



[0021]

[0022] In one aspect, ER formulations of onapristone are provided. The term “extended release” refers to a pharmaceutical compositions or drug formulation that is administered to a patient and has a mechanism to delay the release an active ingredient (i.e., drug). For example, ER pharmaceutical compositions include the active ingredient (e.g., onapristone) and excipients that delay release of the active ingredient (e.g., hydroxypropyl methylcellulose, ethyl cellulose, Eudragit® (Evonik Industries) sustained release formulations (polymethacrylates), polyvinylpyrrolidone (PVP), carrageenan, etc.). The term “immediate release” (IR) refers to pharmaceutical compositions or drug formulations that do not have a mechanism for delaying the release of the active ingredient following administration of the formulation to a patient. Exemplary extended release formulations are provided, for example, in Table 4 herein. The terms “treat,” “prevent,” or similar terms, as used herein, do not necessarily mean 100% or complete treatment or prevention. Rather, these terms refer to various degrees of treatment or prevention of a particular disease (e.g., 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, or 1%) as recognized in the art as being beneficial. The terms “treatment” or “prevention” also refer to delaying onset of a disease for a period of time or delaying onset indefinitely. The term “treatment” or “treating” refers to administering a drug or treatment to a patient or prescribing a drug to a patient where the patient or a third party (e.g., caretaker, family member, or health care professional) administers the drug or treatment

[0023] One aspect provides an extended-release pharmaceutical composition comprising onapristone wherein onapristone is present in an amount from about 2 mg to about 50 mg. Onapristone can be provided, for example, in quantities of 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg, and 50 mg in any suitable extended release formulation (e.g., formulations of Table 4) multiple times per day (e.g., twice per day) or once per day. ER formulations can include excipients that delay the dissolution of the tablet and the subsequent release of onapristone into the gastrointestinal track which then is absorbed into the bloodstream of a patient over time

thereby reducing the C_{max} concentration compared to an IR formulation. A similar release profile can be achieved through the use of an osmotic tablet or a tablet film coated with a polymer that results in an extended release profile of the tablet.

[0024] In another aspect, onapristone ER formulations can be provided in any suitable dosage form (e.g., tablet, capsule, etc.) with a total weight of active ingredients plus excipients ranging from about 50 mg to 400 mg. In another aspect, the tablet can be a matrix tablet, film coated tablet or osmotic pump. In yet another aspect, onapristone ER formulations can be administered to a patient in need of treatment with onapristone once per day, twice per day (BID), or more to achieve the desired dose of onapristone.

[0025] Further aspects provide onapristone ER formulations wherein the purity of the onapristone is at least about 98%. Without being bound by theory, it is believed that using a highly purified form of onapristone in part decreases the liver function test abnormalities resulting in clinical benefits for cancer patients at all doses.

[0026] In another aspect, the ratio of onapristone to inactive excipients in the onapristone ER formulation is about 0.05 (e.g., Table 4) to about 5%.

[0027] Further aspects provide ER formulations wherein the AUC of onapristone following the administration of 10 mg of the onapristone ER formulation to a patient BID is at least about 1578 ng*h/ml over about 8-12 hours. In one aspect, the time period can vary by about plus or minus two hours..

[0028] Another aspect provides onapristone ER formulations where the C_{max} of onapristone following the administration of 10 mg of the onapristone ER formulation to a patient BID is at least about 240 ng/ml over about 8-12 hours. In one aspect, the time period can vary by about plus or minus two hours.

[0029] Another aspect provides onapristone ER formulations where a steady state plasma concentration of onapristone is achieved at about 8 days following the administration of the onapristone ER formulations to a patient twice a day (BID).

[0030] Further aspects provide methods of administering onapristone to a patient comprising administering an onapristone ER formulation twice per day (BID) to a cancer patient, where the onapristone ER formulation comprises of at least about 10 mg to about 50 mg of onapristone. In one aspect, the ER formulation is administered once per day. In another aspect, the onapristone in the onapristone ER formulation is at least about 98% pure.

[0031] In one aspect, the onapristone administered to a patient is at least about 98% pure. In yet another aspect, onapristone in the onapristone ER formulations can be provided, for example, in quantities of 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg, and 50 mg.

[0032] In yet another aspect, the onapristone ER formulations can be administered twice per day (BID) to a human subject in need of treatment, where the onapristone ER formulation comprises of at least about 10 mg to about 50 mg of onapristone. In one aspect, the ER formulation is administered once per day. In another aspect, the disorder is selected from the group consisting of breast cancer, endometrial cancer, prostate cancer, ovarian, uterine endometrioid cancers, and other types of cancer which express the PR.

[0033] In another aspect, the onapristone ER formulation is administered to a human subject having a disorder capable of treatment with onapristone wherein the AUC of onapristone following the administration of 10 mg of the onapristone ER formulation to a patient BID is at least about 1578 ng*h/ml over about 8-12 hours. In another aspect, the time period can vary by about plus or minus two hours.

[0034] In another aspect, the onapristone ER formulation is administered to a human subject having a disorder capable of treatment with onapristone by administering an onapristone ER formulation to the subject twice per day (BID) where the Cmax of onapristone in the human subject is at least about 240 ng/ml over about 8-12 hours. In another aspect, the onapristone ER formulation is administered once per day. In yet another aspect, the time period can vary by about plus or minus two hours.

[0035] In another aspect, an onapristone ER formulation is administered to a human subject having a disorder capable of treatment with onapristone twice per day (BID) where a steady state plasma concentration is achieved at about 8 days.

[0036] PK results for onapristone are available for 52 patients from the a first study (ARN-AR18-CT-101) (Table 1). Variability for onapristone PK is moderate and greater for the IR versus the ER formulation. Onapristone Cmax and AUC values for the ER form are proportional to administered dose (Figures 1 and 2). Based on observed mean AUC values, oral bioavailability for the ER versus the IR formulation is approximately 50% (Figure 24). A later Tmax value for the ER form results in somewhat lower dose-corrected Cmax values for the ER form compared to the IR form. Steady state is attained before day 8 with a mean $t_{1/2}$ of 7.5 hrs.

[0037] Table 1 compares descriptive statistics for the primary onapristone pharmacokinetic exposure parameters following single oral doses from 10 to 50 mg of extended -release onapristone compared to that from 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). Exposure following ER onapristone appears later than that for IR onapristone, consistent with extended release formulations. However, the extended-release aspects are not reflected in the overall duration of exposure. Although study size is small, onapristone exposure generally increases in proportion to ER onapristone dose. Exposure at 50 mg ER onapristone is approximately 20-50% that of 100 mg IR onapristone depending on the formulation. Variability in these parameters is similar for both formulations and across ER onapristone dose levels.

[0038] Table 1 – Summary of PK results for 52 Patients From Study ARN-AR18-CT-101

Form	ER	ER	ER	ER	ER	IR
Dose (mg)	10	20	30	40	50	100
n	12	12	6	10	6	6
AUC_{tau} (ng*h/mL)						
Mean	1578	4228	4856	6833	8966	40800
CV%	75	94	19	65	53	51
C_{max} (ng/mL)						
Mean	240	586	767	870	1459	4296
CV%	67	77	15	67	48	54
t_{max} (hrs)						
Mean	3.4	3.8	3.8	5.2	2.5	1.3
CV%	47	50	51	68	55	61
t_½ (hrs)						
Mean	8.9	7.9	3.9	23.9	11.1	23.6
CV%	120	39	31	183	140	165

[0039] PK results are available in 19 patients from a second study (ARN-AR18-CT-102) and show linear dose relationships for C_{max} and AUC (Table 2) following single oral doses from 10 to 50 mg of extended -release onapristone. Confirming the ARN-AR18-CT-101 study, the ER formulation appears to be performing according to the dose release specifications with a t_½ of approximately 8 hours and a T_{max} of approximately 3-4 hours. Steady state is also achieved within 8 days in this study. Day 29 and 57 data indicate no evidence of accumulation over time, once steady state is reached. Onapristone exposure generally increases less than proportionally with the ER onapristone dose formulation. Variability in these parameters is similar across ER onapristone dose levels.

[0040] Table 2 - Summary of PK results for 19 Patients From Study ARN-AR18-CT-102

Parameter mean (CV%)	Onapristone ER twice-daily dose				
	10mg n=5	20mg n=5	30mg n=3	40mg n=3	50mg n=3
T _{max} , h	4.0 (43)	3.6 (46)	4.0 (50)	3.0 (88)	3.3 (35)
C _{max} , ng/mL	260 (51)	362 (41)	325 (62)	680 (14)	538 (44)
AUC _i , ng/mL*h	7013 (53)	9745 (44)	14380 (18)	17300 (27)	23541 (39)
CL, L/h	1.85 (48)	2.04 (31)	2.13 (18)	2.18 (10)	2.4 (46)
t _{1/2} , h	5.46 (63)	5.61 (30)	9.46 (44)	5.45 (55)	15.9 (53)

[0041] Figures 1 and 2 show the results of an exemplary comparison of the relative systemic onapristone exposure following single oral doses from 10 to 50 mg of extended release onapristone compared to that from 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). Onapristone exposure, assessed by Cmax (Figure 1) and AUC (Figure 2), increases linearly across the ER onapristone dose range and is lower than that for IR onapristone at all ER dose levels. Surprisingly, as disclosed herein, the ER onapristone formulations provided clinical benefit to patients despite lower onapristone exposure.

[0042] Figure 3 shows the results of an exemplary comparison of the degree of onapristone accumulation following twice-daily oral doses from 10 to 50 mg of extended -release onapristone compared to that from daily oral 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). Accumulation for the ER onapristone formulation given twice daily is measurably greater than that for IR onapristone given daily.

[0043] Figures 4A and 4B show exemplary plasma onapristone concentration-time profiles for individual subjects following single oral doses of 50 mg extended -release onapristone compared to that from 100 mg immediate-release onapristone (Study ARN-AR18-CT-101). The profiles for ER onapristone generally reach maximum concentrations more slowly than those for IR onapristone, supporting the extended release of drug from the ER formulation. Concentrations

at all dose levels of ER onapristone are generally lower than those for 100 mg IR onapristone. Surprisingly, as disclosed herein, the ER onapristone formulations provided clinical benefit to patients despite lower onapristone exposure.

[0044] Table 3 – Efficacy In Study ARN-AR18-CT-101

Tumor type	Dose	Response	% change STL	Duration weeks
Serous OC	10	PR	-52	40
Serous OC	50	SD	-7	34
Granulosa OC	40	SD	-24	24
Granulosa OC	30	SD	+5	32
EC	30	SD	-13	30+
EC	20	SD	+5	32
BC	50	SD	-7	32+
BC	20	SD	NA	28
BC	40	SD	-10	24

[0045] Clinical benefit (PR (partial response or SD (stable disease) for ≥ 24 weeks) was observed in ovarian, breast and uterine endometrioid cancers using the onapristone ER formulation. One patient with serous ovarian cancer experienced a PR (32 week duration) and 8 patients had SD for at least 24 weeks (Table 3). The median progression free survival (PFS) was 57.5 days (range 21-281).

[0046] In study ARN-AR18-CT-101, in 52 female patients with PR-positive solid tumors, 9/46 patients (20%) receiving the onapristone ER formulation at doses from 10-50 mg BID demonstrated clinical benefit, vs. 0/6 (0%) patients receiving the 100mg once-daily onapristone IR formulation. Clinical benefit responses, defined as RECIST 1.1 partial response or stable disease for at least 24 weeks, were seen only in patients receiving ER. Of interest, 7/9 of the

patients with clinical benefit (78%) received doses below the established 100mg IR dose and the patient with a partial response was treated at the lowest ER dose level, 10mg BID.

[0047] With respect to ARN-AR18-CT-102, 2 of 21 patients with prostate cancer had SD after week 12. Median duration of treatment was 8 weeks.

EXAMPLES

[0048] The following non-limiting examples illustrate aspects described herein. Not every element described herein is required. Indeed, a person of skill in the art will find numerous additional uses of and variations to the methods described herein, which the inventors intend to be limited only by the claims. All references cited herein are incorporated by reference in their entirety.

[0049] Example 1

[0050] ER Formulations

[0051] Table 4 – Onapristone Extended-Release Formulations

Component	Amount per tablet (mg)				Function
	2.5 mg	5 mg	10 mg	20 mg	
Onapristone	2.50	5.00	10.00	20.00	Active
Lactose monohydrate	10.25	20.50	41.00	82.00	Filler
Microcrystalline cellulose	10.25	20.50	41.00	82.00	Filler
Pregelatinized starch	10.00	20.00	40.00	80.00	Disintegrant
Hydroxypropyl methylcellulose	16.50	33.00	66.00	132.00	Binder / modified release agent
Colloidal silicon dioxide	0.25	0.50	1.00	2.00	Glidant
Magnesium stearate	0.25	0.50	1.00	2.00	Lubricant
Tablet weight (mg)	50.00	100.00	200.00	400.00	

[0052] Table 4 provide exemplary onapristone extended release formulations. In one aspect, the tablets can be provided to a patient alone or in any desired combination to achieve the desired dose.

[0053] Example 2 – Preparing Exemplary Onapristone ER Formulations

[0054] Onapristone extended-release formulations can be prepared by the following exemplary method:

[0055] Step 1: De-lump onapristone drug substance by milling or by passing through a wire screen followed by further passing the resulting de-lumped onapristone through a wire screen of appropriate mesh size (e.g., 425 or 710 microns).

[0056] Step 2: Screen the colloidal silicon dioxide and approximately half of the pregelatinized starch separately through a screen of appropriate mesh size (e.g., 425 or 710 microns) into a stainless steel blending container. The previously-screened onapristone drug substance from Step 1 is added to this blend.

[0057] Step 3: The mixture is blended and screened through a screen of appropriate mesh size (e.g., 425 or 710 microns).

[0058] Step 4: The remaining pregelatinized starch is screened through a screen of appropriate mesh size (e.g., 425 or 710 microns) into the stainless steel blending container (from Step 2). The previously screened mixture from Step 3 is added to the container.

[0059] Step 5: The mixture is blended to achieve a homogenous mix.

[0060] Step 6: Approximately half of the microcrystalline cellulose, half of the lactose monohydrate and half of the hydroxypropyl methylcellulose are separately screened into a larger stainless steel blending container through a screen of appropriate mesh size (e.g., 425 or 710 microns). The blend from Step 5 is added to this container, and the remaining microcrystalline cellulose, lactose monohydrate and hydroxypropyl methylcellulose are screened into the container through a screen of appropriate mesh size (e.g., 425 or 710 microns).

[0061] Step 7: The mixture is blended further to achieve a homogeneous mix.

[0062] Step 8: The mixture from Step 7 is co-screened with magnesium stearate through a screen of appropriate mesh size (e.g., 425 or 710 microns) into the container from Step 4.

[0063] Example 3

[0064] Patients and Methods

[0065] *Eligibility*

[0066] Inclusion criteria included:

[0067] (1) post-menopausal female patients \geq 18 years of age that have been previously treated recurrent or metastatic progesterone receptor-expressing cancer (e.g., endometrial, ovarian, breast cancer or uterine sarcoma) with evaluable disease per Response Evaluation Criteria In Solid Tumors, version 1.1 (RECIST 1.1);

[0068] (2) patients having available tissue blocks or biopsy specimens to determine progesterone receptor (PR) and activated progesterone receptor (APR) status; and

[0069] (3) patients having Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and signed informed consent.

[0070] The PR determination for inclusion purposes was performed on archived tissue blocks in the pathology department of each participating center. Central PR/APR evaluation was planned, but retrospective relative to inclusion and treatment.

[0071] Key exclusion criteria included significantly impaired liver or kidney function, creatinine clearance lower than 60 mL/min, total bilirubin $>$ upper limit of normal (ULN), alkaline phosphatase $>$ ULN (or $>$ 2.5 \times ULN with liver or $>$ 5 \times ULN with bone metastases), ALT/AST $>$ ULN (or $>$ 2.5 \times ULN with liver metastases), QTcF $>$ 480 msec, chronic inflammatory liver condition, severe concomitant disease, uncontrolled brain metastases, inadequate washout from previous therapy, inability to swallow or absorb tablets, use of inhibitors, inducers or substrates of CYP3A4, or use of progestin-based hormone replacement therapy.

[0072] Example 4

[0073] Study Design and Treatment

[0074] The study was an open-label, multicenter, randomized, parallel-group, two part phase 1-2 study with phase I part of the trial discussed herein. To determine the recommended phase 2 dose (RP2D), patients enrolled in this phase 1 study were randomized in parallel fashion to six (6) cohorts: five (5) cohorts of ER ONA tablets (10 mg BID, 20 mg BID, 30 mg BID, 40 mg BID, 50 mg BID) and one (1) cohort using the IR tablet formulation (100 mg QD). The trial was conducted in five (5) centers in France (registered on ClinicalTrials.gov as NCT02052128).

[0075] The study was approved by the Ile de France III Comité pour la Protection des Personnes (a French national ethics committee), the ANSM (French regulatory authority) and individual site scientific review boards, and written informed consent was obtained from each study patient.

[0076] Highly purified ONA tablets can be by standard pharmaceutical chemistry purification methods by those skilled in the art. ER formulation with release kinetics from 10-12 hours depending on tablet dose. The original study design included a 20-patient expansion component. An 8-week dose-limiting toxicity (DLT) observation period was utilized to characterize thoroughly the safety profile, as previous ONA studies demonstrated a spike in the LFTs at approximately 6 weeks of treatment.

[0077] Patients were treated until documented progressive disease (PD) or intolerance to medication. We consider the design of this study to be in agreement with the recently-proposed guidance for phase 1 protocols for dose escalation [Iasonos 2015].

[0078] Example 5

[0079] Pharmacokinetics Methods

[0080] Blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 12 (before next BID dose), and 24 (before next dose- for 100 mg IR only) hours post- ONA, as well as hour 0 on days 8, 29 and 57 (just before drug intake). Plasma concentrations of ONA, mono-demethylated onapristone (M1) and other metabolites in plasma and urine were analyzed with a validated ultra-performance liquid chromatography with tandem mass spectrometry detection (UPLC-MS/MS) assay.

Pharmacokinetic modeling was performed using Monolix software in order to estimate PK parameters Cmax, Tmax, AUC0-last, AUC0-8, t1/2, Vd, CL, and Vc.

[0081] Although the above description refers to particular aspects, it is to be understood that these aspects are merely illustrative. It will be apparent to those skilled in the art that various modifications and variations can be made to the polymorphic forms and methods described herein. Thus, it is intended that the present description include modifications and variations that are within the scope of the appended claims and their equivalents.

[0082] Throughout the specification and claims, unless the context requires otherwise, the word “comprise” or variations such as “comprises” or “comprising”, will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

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CLAIMS

What is claimed is:

1. A method of administering onapristone to a patient having a cancer comprising administering an extended-release onapristone pharmaceutical composition to the patient, wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate.
2. The method of claim 1, wherein the extended-release onapristone pharmaceutical composition is administered twice per day.
3. The method of claim 1, wherein the onapristone is at least about 98% pure.
4. The method of claim 1, wherein the amount of onapristone in the extended-release onapristone pharmaceutical composition is selected from the group consisting of about 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg and 50 mg.
5. The method of claim 1, wherein the cancer expresses the progesterone receptor.
6. The method of claim 5, wherein the cancer is selected from the group consisting of breast, prostate, ovarian, and uterine endometrioid cancers.
7. A method of treating a human subject having a cancer which expresses the progesterone receptor comprising administering an extended-release onapristone pharmaceutical composition to the human subject wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate, and wherein the AUC of onapristone following the administration of the extended-release onapristone

pharmaceutical composition is at least about 1578 ng*h/ml over about 8-12 hours.

8. The method of claim 7, wherein the extended-release onapristone pharmaceutical composition is administered to the human subject once per day.
9. A method of treating a human subject having a cancer which expresses the progesterone receptor comprising administering an extended-release onapristone pharmaceutical composition wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate, and wherein the Cmax of onapristone following the administration of the extended-release onapristone pharmaceutical composition in the human subject is at least about 240 ng/ml over about 8-12 hours.
10. The method of claim 9, wherein the extended-release onapristone pharmaceutical composition is administered to the human subject once per day.
11. A method of treating a human subject having a cancer which expresses the progesterone receptor comprising administering an extended-release pharmaceutical composition wherein the extended-release onapristone pharmaceutical composition comprises about 5% (wt/wt) onapristone, about 20.5% (wt/wt) lactose monohydrate, about 20.5% (wt/wt) microcrystalline cellulose, about 20% (wt/wt) pregelatinized starch, about 33% (wt/wt) hydroxypropyl methylcellulose, about 0.5% silicon dioxide, and about 0.5% magnesium stearate, and wherein a steady-state plasma concentration of onapristone following the administration of the extended-release onapristone pharmaceutical composition in the human subject is achieved at about 8 days.
12. The method of claim 11, wherein the extended-release onapristone pharmaceutical composition is administered to the human subject once per day.

13. The method of claim 7, wherein the cancer which expresses the progesterone receptor is selected from group consisting of breast cancer, endometrial cancer, prostate cancer, ovarian, and uterine cancers.
14. The method of claim 1, wherein the extended-release onapristone pharmaceutical composition is administered once per day.
15. The method of claim 7, wherein the extended-release onapristone pharmaceutical composition is administered twice per day.
16. The method of claim 7, wherein the amount of onapristone in the extended-release onapristone pharmaceutical composition is selected from the group consisting of about 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg and 50 mg.
17. The method of claim 9, wherein the extended-release onapristone pharmaceutical composition is administered twice per day.
18. The method of claim 9, wherein the amount of onapristone in the extended-release onapristone pharmaceutical composition is selected from the group consisting of about 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg and 50 mg.
19. The method of claim 11, wherein the extended-release onapristone pharmaceutical composition is administered twice per day.
20. The method of claim 11, wherein the amount of onapristone in the extended-release onapristone pharmaceutical composition is selected from the group consisting of about 2 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 25 mg, 37.5 mg and 50 mg.
21. The method of claim 20, wherein the AUC of onapristone following the administration of the extended-release onapristone pharmaceutical composition is at least about 1578 ng*h/ml over about 8-12 hours.
22. The method of claim 20, wherein the Cmax of onapristone in the human subject is at least about 240 ng/ml over about 8-12 hours following the administration of the extended-release onapristone pharmaceutical composition to the human subject.

Figure 1

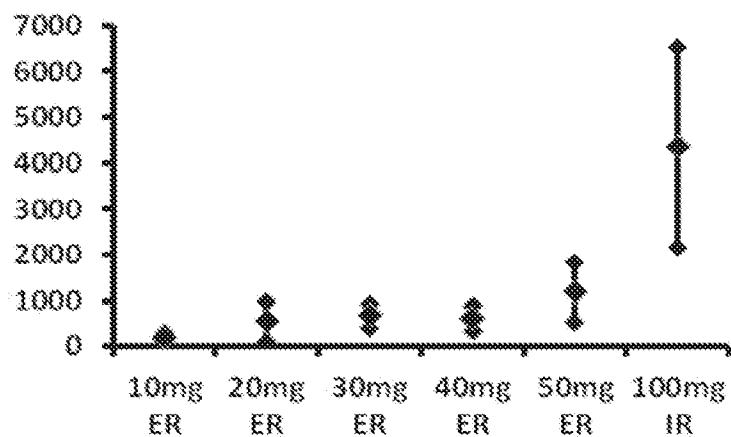
Onapristone C_{max} vs Dose

Figure 2

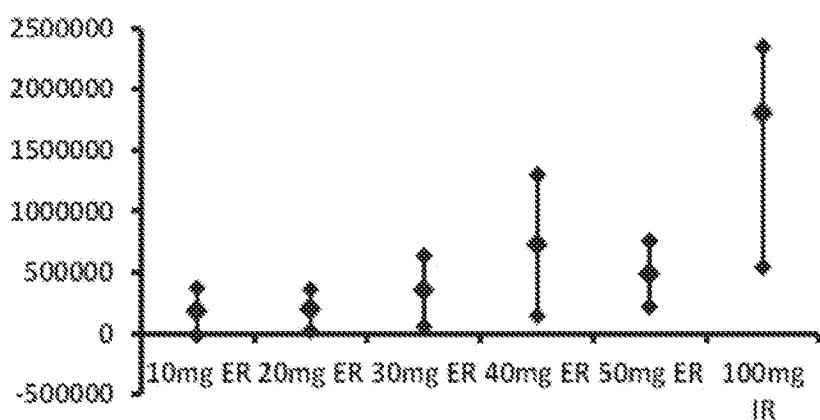
Onapristone AUC vs Dose

Figure 3

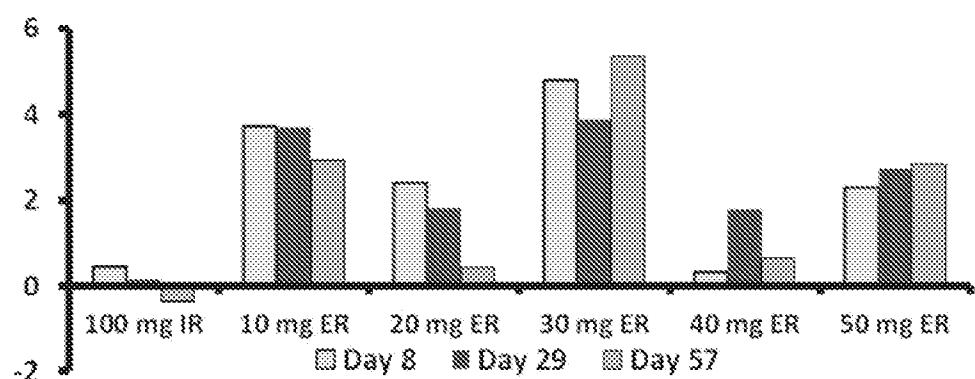


Figure 4A

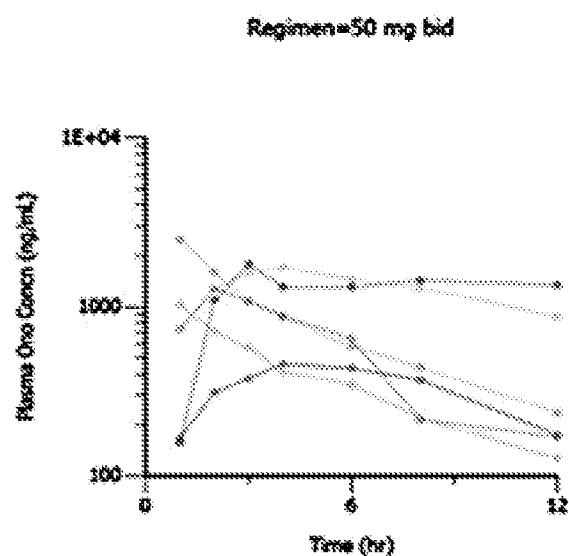


Figure 4B

