ANTICANCER COMPOSITIONS

The present invention concerns pharmaceutical formulations of ARN-509, 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, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer. In one aspect, these formulations comprise a solid dispersion of ARN-509 and HPMCAS. In one aspect, the solid dispersion of ARN-509 and HPMCAS is obtainable, in particular is obtained, by melt-extruding a mixture comprising ARN-509 and HPMCAS and optionally subsequently milling said melt-extruded mixture. In one aspect, the solid dispersion of ARN-509 and HPMCAS is obtainable, in particular is obtained, by spray drying a mixture comprising ARN-509 and HPMCAS in a suitable solvent.

The solid dispersion of ARN-509 and HPMCAS may be further formulated with a pharmaceutically acceptable carrier into a pharmaceutical formulation, such formulation providing improved stability or improved shelf life. With the formulation of the present invention the pill burden for the patient, in particular the cancer patient, can be reduced, and hence therapy adherence and therapy efficiency can be improved.

FIGURES

Fig. 1 : XRD pattern of ARN-509 Form B.
Fig. 2 : IR spectrum of ARN-509 Form B.
Fig. 3 : DSC curve of ARN-509 Form B.

DETAILED DESCRIPTION

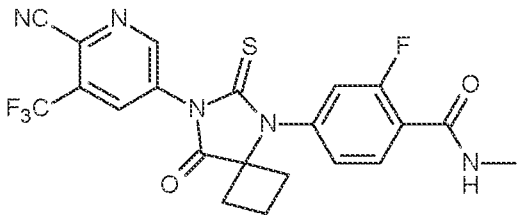
ARN-509 is a potent and specific antagonist of the androgen receptor (AR). ARN-509's mechanism of action is antagonism of androgen receptor signaling through inhibition of AR nuclear translocation and DNA binding to androgen response elements.

The actions of androgens with androgen receptors have been implicated in a number of diseases or conditions, such as androgen dependent cancers, virilization in women, and

acne, among others. Compounds that diminish the effects of androgens with androgen receptors and/or lower the concentrations of androgen receptors find use in the treatment of diseases or conditions in which androgen receptors play a role.

AR-related diseases or conditions include, but are not limited to, benign prostate hyperplasia, hirsutism, acne, adenomas and neoplasias of the prostate, benign or malignant tumor cells containing the androgen receptor, hyperpilosity, seborrhea, endometriosis, polycystic ovary syndrome, androgenic alopecia, hypogonadism, osteoporosis, suppression of spermatogenesis, libido, cachexia, anorexia, androgen supplementation for age related decreased testosterone levels, prostate cancer, breast cancer, endometrial cancer, uterine cancer, hot flashes, Kennedy's disease muscle atrophy and weakness, skin atrophy, bone loss, anemia, arteriosclerosis, cardiovascular disease, loss of energy, loss of well-being, type 2 diabetes, and abdominal fat accumulation. Given the central role of AR in prostate cancer development and progression, ARN-509 is useful for the treatment of cancer, in particular prostate cancer, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer.

The chemical structure of ARN-509 is:



ARN-509 or 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-*N*-methylbenzamide is currently in clinical development as a nonaqueous, lipid-based solution that is filled into softgel capsules, each containing 30 mg ARN-509. The daily dose being studied is 240 mg/day by oral administration (or 8 softgel capsules). It has been found that in use, the softgel capsules containing ARN-509 have a shelf life of only 6 months and need cold chain storage.

An aspect of the invention relates to pharmaceutical formulations, in particular solid pharmaceutical formulations, more in particular solid pharmaceutical formulations for oral adminstration of ARN-509, where such formulations have an improved stability, a longer shelf life, or provide for a reduced pill burden for the patient, in particular the cancer patient. The pharmaceutical formulations of the present invention provide a means to increase therapy adherence and therapy efficiency.

An aspect of the invention is a solid dispersion comprising ARN-509 and HPMCAS.

HPMCAS or hydroxypropyl methylcellulose acetate succinate or hypromellose acetate succinate (CAS number 71138-97-1) is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose (IUPAC name : cellulose, 2-hydroxypropyl methyl ether, acetate, hydrogen butanedioate). Different grades are available differentiated based on degree/ratio of substitution (acetyl content, succinoyl content) and particle size (micronized and granular). In an aspect of the invention, the HPMCAS in the dispersions with ARN-509 is HPMCAS LG (granular grade) or HPMCAS LF (micronized grade) (Shin-Etsu Chemical Co., Ltd), in particular HPMCAS LG.

An aspect of the invention is a solid dispersion comprising ARN-509 and HPMCAS LG.

An aspect of the invention is a solid dispersion comprising ARN-509 and HPMCAS LF.

An aspect of the invention is a solid dispersion consisting of ARN-509 and HPMCAS.

An aspect of the invention is a solid dispersion consisting of ARN-509 and HPMCAS LG.

An aspect of the invention is a solid dispersion consisting of ARN-509 and HPMCAS LF.

A preferred grade of HPMCAS in the solid dispersions of the invention is HPMCAS LG, because of its better and safer handling properties.

In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS in the solid dispersion as described herein is in the range from 1 : 1 to 1 : 10, preferably

from 1 : 1 to 1 : 5, more preferably from 1 : 1 to 1 : 3 or from 1 : 2 to 1 : 3. In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2. In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS is 1:3. In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2. In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:3. In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2. In an aspect of the invention, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:3.

An aspect of the invention is a particle consisting of a solid dispersion as described herein.

An aspect of the invention is a particle consisting of a solid dispersion comprising ARN-509 and HPMCAS, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

An aspect of the invention is a particle consisting of a solid dispersion comprising ARN-509 and HPMCAS LG, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

An aspect of the invention is a particle consisting of a solid dispersion comprising ARN-509 and HPMCAS LF, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

An aspect of the invention is a particle consisting of a solid dispersion consisting of ARN-509 and HPMCAS, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

An aspect of the invention is a particle consisting of a solid dispersion consisting of ARN-509 and HPMCAS LG, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

An aspect of the invention is a particle consisting of a solid dispersion consisting of ARN-509 and HPMCAS LF, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

An aspect of the invention is a particle comprising a solid dispersion as described hereinabove.

An aspect of the invention is a particle comprising a solid dispersion comprising ARN-509 and HPMCAS, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

An aspect of the invention is a particle comprising a solid dispersion comprising ARN-509 and HPMCAS LG, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

An aspect of the invention is a particle comprising a solid dispersion comprising ARN-509 and HPMCAS LF, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

An aspect of the invention is a particle comprising a solid dispersion consisting of ARN-509 and HPMCAS, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

An aspect of the invention is a particle comprising a solid dispersion consisting of ARN-509 and HPMCAS LG, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

An aspect of the invention is a particle comprising a solid dispersion consisting of ARN-509 and HPMCAS LF, in particular wherein the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

In an aspect of the invention, the particles as described herein are obtainable, in particular are obtained, by melt-extruding a mixture comprising ARN-509 and HPMCAS and subsequently milling said melt-extruded mixture. In an aspect, the particles as described herein are obtainable, in particular are obtained, by melt-extruding a mixture consisting of ARN-509 and HPMCAS and subsequently milling said melt-extruded mixture. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

In an aspect of the invention, the particles as described herein are obtainable, in particular are obtained, by melt-extruding a mixture comprising ARN-509 and

HPMCAS LG and subsequently milling said melt-extruded mixture. In an aspect, the particles as described herein are obtainable, in particular are obtained, by melt-extruding a mixture consisting of ARN-509 and HPMCAS LG and subsequently milling said melt-extruded mixture. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

In an aspect of the invention, the particles as described herein are obtainable, in particular are obtained, by melt-extruding a mixture comprising ARN-509 and HPMCAS LF and subsequently milling said melt-extruded mixture. In an aspect, the particles as described herein are obtainable, in particular are obtained, by melt-extruding a mixture consisting of ARN-509 and HPMCAS LF and subsequently milling said melt-extruded mixture. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

In an aspect of the invention, the particles as described herein are obtainable, in particular are obtained, by spray drying a mixture comprising ARN-509 and HPMCAS in a suitable solvent. In an aspect, the particles as described herein are obtainable, in particular are obtained, by spray drying a mixture consisting of ARN-509 and HPMCAS in a suitable solvent. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

In an aspect of the invention, the particles as described herein are obtainable, in particular are obtained, by spray drying a mixture comprising ARN-509 and HPMCAS LG in a suitable solvent. In an aspect, the particles as described herein are obtainable, in particular are obtained, by spray drying a mixture consisting of ARN-509 and HPMCAS LG in a suitable solvent. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

In an aspect of the invention, the particles as described herein are obtainable, in particular are obtained, by spray drying a mixture comprising ARN-509 and HPMCAS LF in a suitable solvent. In an aspect, the particles as described herein are obtainable, in particular are obtained, by spray drying a mixture consisting of ARN-509 and HPMCAS LF in a suitable solvent. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS LG. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS LG. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS LF. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS LF. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles comprising a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles comprising a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS is 1:2 or 1:3. In an aspect, the particles are obtainable, in particular are obtained, by spray drying as described herein. In an aspect, the particles are obtainable, in particular are obtained, by melt extrusion as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles consisting of a solid dispersion, said

solid dispersion comprising ARN-509 and HPMCAS. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles consisting of a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS. In an aspect, the particles are obtainable, in particular are obtained, by spray drying as described herein. In an aspect, the particles are obtainable, in particular are obtained, by melt extrusion as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles comprising a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS LG. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles comprising a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS LG. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3. In an aspect, the particles are obtainable, in particular are obtained, by spray drying as described herein. In an aspect, the particles are obtainable, in particular are obtained, by melt extrusion as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles comprising a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS LF. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles comprising a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS LF. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3. In an aspect, the particles are obtainable, in particular are obtained, by spray drying as described herein. In an aspect, the particles are obtainable, in particular are obtained, by melt extrusion as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles consisting of a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS LG. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles consisting of a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS LG. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LG is 1:2 or 1:3. In an aspect, the particles are obtainable, in particular are obtained, by spray drying as described herein. In an aspect, the particles are obtainable, in particular are obtained, by melt extrusion as described herein.

An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles consisting of a solid dispersion, said solid dispersion comprising ARN-509 and HPMCAS LF. An aspect of the invention is a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles consisting of a solid dispersion, said solid dispersion consisting of ARN-509 and HPMCAS LF. In an aspect, the weight-by-weight ratio of ARN-509 : HPMCAS LF is 1:2 or 1:3. In an aspect, the particles are obtainable, in particular are obtained, by spray drying as described herein. In an aspect, the particles are obtainable, in particular are obtained, by melt extrusion as described herein.

An aspect of the invention is a solid dispersion as described herein wherein no surfactant is present.

An aspect of the invention is a particle as described herein wherein no surfactant is present.

An aspect of the invention is a pharmaceutical formulation as described herein wherein no surfactant is present.

An aspect of the invention is a solid dispersion as described herein wherein ARN-509 is the only active pharmaceutical ingredient.

An aspect of the invention is a particle as described herein wherein ARN-509 is the only active pharmaceutical ingredient.

An aspect of the invention is a pharmaceutical formulation as described herein wherein ARN-509 is the only active pharmaceutical ingredient.

In the solid dispersions or particles or pharmaceutical formulations as described herein ARN-509 is present in base form or as a pharmaceutically acceptable addition salt, in particular as a pharmaceutically acceptable acid addition salt. Preferably, ARN-509 is present in base form.

The pharmaceutically acceptable addition salts are meant to comprise the therapeutically active non-toxic salt forms. The acid addition salt forms can be obtained by treating the base form of ARN-509 with an appropriate acid, such as inorganic acids, including but not limited to, hydrohalic acids, e.g. hydrochloric acid,

hydrobromic acid and the like acids; sulfuric acid; nitric acid; phosphoric acid; metaphosphoric acid and the like acids; or organic acids, including but not limited to, acetic acid, trifluoroacetic acid, trimethylacetic acid, propanoic acid, hydroxyacetic acid, 2-hydroxypropanoic acid, 2-oxopropanoic acid, glycolic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, mandelic acid, tartaric acid, 2-hydroxy-1,2,3-propanetricarboxylic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2- hydroxyethanesulfonic acid, benzoic acid, cinnamic acid, hydrocinnamic acid, benzenesulfonic acid, 4-methylbenzene-sulfonic acid, 2- naphthalenesulfonic acid, cyclohexanesulfamic acid, 2-hydroxybenzoic acid, 4-amino-2-hydroxybenzoic acid, hexanoic acid, cyclopentanepropionic acid, 3-(4-hydroxybenzoyl)benzoic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-l-carboxylic acid, glucoheptonic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

Also included are the hydrates, the solvent addition forms and mixtures thereof which ARN-509 and its salts are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like, for instance an ethanolate.

In general, doses employed for adult human treatment are typically in the range from 0.01 mg to 5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In another aspect, doses employed for adult human treatment are from about 100 mg to about 500 mg per day. In another aspect, the dose employed for adult human treatment is 240 mg per day. The exact dosage and frequency of administration of ARN-509 may depend on the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is known to those skilled in the art. Furthermore, it is evident that said daily amounts may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing ARN-509. The doses mentioned herein are therefore only a guideline and are not intended to limit the scope or use of the invention to any extent. In an aspect of the invention, the daily dose is conveniently presented in a single dose or in divided doses

administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day. In an aspect of the invention, the daily dose is administered in 4 divided doses. In an aspect of the invention, the daily dose is administered in 4 divided doses administered simultaneously (or over a short period of time). In an aspect of the invention, the daily dose is administered in 3 divided doses. In an aspect of the invention, the daily dose is administered in 3 divided doses administered simultaneously (or over a short period of time). In an aspect of the invention, the daily dose is administered in 2 divided doses. In an aspect of the invention, the daily dose is administered in 2 divided doses administered simultaneously (or over a short period of time).

In an aspect of the invention, the pharmaceutical formulation comprises 240 mg of ARN-509.
In an aspect of the invention, the pharmaceutical formulation comprises 120 mg of ARN-509.
In an aspect of the invention, the pharmaceutical formulation comprises 60 mg of ARN-509.

In an aspect of the invention, the pharmaceutical formulation comprises 240 mg of ARN-509. The pharmaceutical formulation is administered once daily.

In an aspect of the invention, the pharmaceutical formulation comprises 120 mg of ARN-509. Two of said formulations are administered daily, preferably simultaneously (or over a short period of time).

In an aspect of the invention, the pharmaceutical formulation comprises 60 mg of ARN-509. Four of said formulations are administered daily, preferably simultaneously (or over a short period of time).

The formulation of the present invention can also be used in combination with another anticancer agent, in particular with another anti prostate cancer agent, more in particular with an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17), in particular abiraterone acetate. The formulation of the present invention can further be combined with prednisone.
Thus, the present invention also relates to a combination of a pharmaceutical formulation according to the invention and another anticancer agent, in particular another anti prostate cancer agent, more in particular an androgen biosynthesis

inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17), in particular abiraterone acetate.
Said combination may further comprise prednisone.

The term "a solid dispersion" means a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion will be called "a solid solution" herein. Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. This advantage can probably be explained by the ease with which said solid solutions can form liquid solutions when contacted with a liquid medium such as gastric juice. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid dispersion" also relates to a system in a solid state comprising at least two components (a) and (b) and having domains or small regions wherein amorphous, microcrystalline or crystalline (a), or amorphous, microcrystalline or crystalline (b), or both, are dispersed more or less evenly in another phase comprising (b), or (a), or a solid solution comprising (a) and (b). Said domains are regions distinctively marked by some physical feature, small in size compared to the size of the system as a whole, and evenly and randomly distributed throughout the system.

Preferred are solid dispersions or particles as described herein wherein ARN-509 is in a non-crystalline phase as these have an intrinsically faster dissolution rate than those wherein part or all of ARN-509 is in a microcrystalline or crystalline form.

Alternatively, the solid dispersions may be in the form of a dispersion wherein amorphous or microcrystalline ARN-509 or amorphous or microcrystalline HPMCAS is dispersed more or less evenly in a solid solution comprising ARN-509 and HPMCAS.

In an aspect of the invention ARN-509 is present in the solid dispersions as described herein in amorphous form.

In an aspect of the invention the solid dispersion as described herein is a solid solution.

Various techniques exist for preparing the solid dispersions of the invention including melt-extrusion (e.g. hot melt extrusion), spray-drying and solution-evaporation, in particular hot melt-extrusion and spray-drying, spray-drying being preferred.

The particles according to the invention can be prepared by first preparing a solid dispersion of the components, and then optionally grinding or milling said dispersion.

The melt-extrusion process comprises the following steps :

a) mixing ARN-509 and HPMCAS,
b) optionally blending additives with the thus obtained mixture,
c) heating the thus obtained blend until one obtains a homogenous melt,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies.

The terms "melt" and "melting" do not only mean the alteration from a solid state to a liquid state, but can also refer to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less homogeneously into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

One important parameter of melt extrusion is the temperature at which the melt-extruder is operating. For the melt extrusion process of the present invention, the operating temperature preferably ranges between about 160°C and about 190°C, more preferably ranges between about 160°C and 175°C. The lower temperature limit is defined by the point at which ARN-509 is still melting during extrusion with a given set of extrusion conditions. When ARN-509 is not completely molten, the extrudate may not provide the desired bioavailability. When the viscosity of the mixture is too high, the process of melt extrusion will be difficult. At higher temperatures the components may decompose to an unacceptable level. A person skilled in the art will recognize the most appropriate temperature range to be used.

The throughput rate is also of importance because the components may start to decompose when they remain too long in contact with the heating element.

It will be appreciated that the person skilled in the art will be able to optimize the parameters of the melt extrusion process within the above given ranges. The working temperatures will also be determined by the kind of extruder or the kind of configuration within the extruder that is used. Most of the energy needed to melt, mix and dissolve the components in the extruder can be provided by the heating elements. However, the friction of the material within the extruder may also provide a substantial amount of energy to the mixture and aid in the formation of a homogenous melt of the components.

A person skilled in the art will recognize the most appropriate extruder, such as, for example, a single screw, a twin screw extruder or a multi-screw extruder, for the preparation of the subject-matter of the present invention.

Spray-drying of a mixture of the components in a suitable solvent also yields a solid dispersion of said components or particles comprising or consisting of a solid dispersion of said components and may be a useful alternative to the melt-extrusion process, particularly in those cases where the HPMCAS is not sufficiently stable to withstand the extrusion conditions and where residual solvent can effectively be removed from the solid dispersion. Yet another possible preparation consists of preparing a mixture of the components in a suitable solvent, pouring said mixture onto a large surface so as to form a thin film, and evaporating the solvent therefrom.

Solvents suitable for spray-drying can be any organic solvent in which ARN-509 and HPMCAS, in particular HPMCAS LG or HPMCAS LF, are miscable. In an aspect of the invention, the boiling point of the solvent is lower than the Tg (glass transition temperature) of the solid dispersion. In addition, the solvent should have relatively low toxicity and be removed from the dispersion to a level that is acceptable according to The International Committee on Harmonization (ICH) guidelines. Removal of solvent to this level may require a post drying step such as for instance tray-drying, subsequent to the spray-drying process. Solvents include alcohols such as methanol, ethanol, n-propanol, iso-propanol, and butanol, in particular methanol; ketones such as acetone, methyl ethyl ketone and methyl iso-butyl ketone; esters such as ethyl acetate and propylacetate; and various other solvents such as acetonitrile, dichloromethane,

toluene, and 1,1,1-trichloroethane. Lower volatility solvents such as dimethyl acetamide or dimethylsulfoxide can also be used. In an aspect of the invention, the solvent suitable for spray drying is a mixture of solvents. In an aspect of the invention the solvent for spray drying is a mixture of an alcohol and dichloromethane, in particular a mixture of methanol and dichloromethane, more in particular a mixture of methanol and dichloromethane 6:4 (w:w) or 5:5 (w/w), 6:4 (w:w) being preferred.

The particles as described herein have a d^{50} of about 1500 μm, of about 1000 μm, of about 500 μm, of about 400 μm, of about 250 μm, of about 200μm, of about 150μm, of about 125 μm, of about 100μm, of about 70 μm, of about 65μm, of about 60μm, of about 55μm, of about 50μm, of about 45μm, of about 40μm, of about 35μm, of about 30μm, of about 25μm, or of about 20μm. Particles obtained by spray drying have preferably a d^{50}-value falling in the range from about 20μm to about 100μm, in particular a d^{50}-value falling in the range from about 20μm to about 70μm, more in particular a d^{50}-value of about 20μm, of about 25μm, of about 30μm, of about 35μm, of about 40μm, of about 45μm, of about 50μm, of about 55μm, of about 60μm, of about 65μm, or of about 70μm.

As used herein, the term d^{50} has its conventional meaning as known to the person skilled in the art and can be measured by art-known particle size measuring techniques such as, for example, sedimentation field flow fractionation, photon correlation spectroscopy, laser diffraction or disk centrifugation. The d^{50} mentioned herein may be related to volume distributions of the particles. In that instance, by "a d^{50} of 50 μm" it is meant that at least 50% of the volume of the particles has a particle size of less than 50 μm. The same applies to the other particle sizes mentioned. In a similar manner, the d^{50} particle size may be related to weight distributions of the particles. In that instance, by "d^{50} of 50 μm" it is meant that at least 50% of the weight of the particles has a particle size of less than 50 μm. The same applies to the other particle sizes mentioned. Usually volume and weight distribution result in the same or about the same value for the average particle size.

The particle size can be an important factor determining the tabletting speed, in particular the flowability and therefore the manufacturability on a large scale of a particular dosage form or formulation, and the quality of the final product. For instance, for capsules, the particle size may range preferably from about 100 to about 1500 μm (d^{50}); for tablets the particle size is preferably less than 250 μm, more

preferably less than 100 μm (d^{50}). Too small particles (< 10-20 μm) often cause sticking on the tablet punches and manufacturability issues.

The particles or solid dispersions as described herein may further comprise one or more pharmaceutically acceptable excipients such as, for example, plasticizers, flavors, colorants, preservatives and the like. Especially in case of preparation by hot melt extrusion, said excipients should not be heat-sensitive, in other words, they should not show any appreciable degradation or decomposition at the working temperature of the melt-extruder.

Suitable plasticizers are pharmaceutically acceptable and include low molecular weight polyalcohols such as ethylene glycol, propylene glycol, 1,2 butylene glycol, 2,3-butylene glycol, styrene glycol; polyethylene glycols such as diethylene glycol, triethylene glycol, tetraethylene glycol; other polyethylene glycols having a molecular weight lower than 1,000 g/mol; polypropylene glycols having a molecular weight lower than 200 g/mol; glycol ethers such as monopropylene glycol monoisopropyl ether; propylene glycol monoethyl ether; diethylene glycol monoethyl ether; ester type plasticizers such as triethyl citrate, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, allyl glycollate; and amines such as monoethanolamine, diethanolamine, triethanolamine, monoisopropanolamine; triethylenetetramine, 2-amino-2-methyl-1,3-propanediol and the like. Of these, the low molecular weight polyethylene glycols, ethylene glycol, low molecular weight polypropylene glycols and especially propylene glycol are preferred.
In an aspect of the invention, the particles or solid dispersions as described herein do not contain a plasticizer.

The solid dispersions or the particles of the present invention can be formulated into pharmaceutical formulations comprising a therapeutically effective amount of ARN-509. Although, at first instance, pharmaceutical formulations for oral administration such as tablets and capsules are envisaged, the solid dispersions or the particles of the present invention can also be used to prepare pharmaceutical formulations e.g. for rectal administration. Preferred formulations are those adapted for oral administration shaped as a tablet. They can be produced by conventional tabletting techniques with conventional ingredients or excipients (pharmaceutically acceptable carrier) and with conventional tabletting machines. In order to facilitate the swallowing of such a formulation by a mammal, it is advantageous to give the

formulations, in particular tablets, an appropriate shape. A film coat on the tablet may further contribute to the ease with which it can be swallowed.

The formulations of the invention, in particular the tablets, may include one or more conventional excipients (pharmaceutically acceptable carrier) such as disintegrants, diluents, fillers, binders, buffering agents, lubricants, glidants, thickening agents, sweetening agents, flavors, and colors. Some excipients can serve multiple purposes. Preferably, the formulations of the present invention include a disintegrant, a diluent or filler, a lubricant and glidant.

Suitable disintegrants are those that have a large coefficient of expansion. Examples thereof are hydrophilic, insoluble or poorly water-soluble crosslinked polymers such as crospovidone (crosslinked polyvinylpyrrolidone) and croscarmellose sodium (crosslinked sodium carboxymethylcellulose). The amount of disintegrant in the tablets according to the present invention may conveniently range from about 3 to about 15 % (w/w) and preferably range from about 3 to 7 %, in particular is about 5 % (w/w). Because disintegrants by their nature yield sustained release formulations when employed in bulk, it is advantageous to dilute them with an inert substance called a diluent or filler.

A variety of materials may be used as diluents or fillers. Examples are lactose monohydrate, anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (e.g. micro-crystalline cellulose (Avicel™), silicified microcrystalline cellulose), dihydrated or anhydrous dibasic calcium phosphate, and others known in the art, and mixtures thereof (e.g. spray-dried mixture of lactose monohydrate (75 %) with microcrystalline cellulose (25 %) which is commercially availble as Microcelac™). Preferred is microcrystalline cellulose and silicified microcrystalline cellulose. The amount of diluent or filler in the tablets may conveniently range from about 20 % to about 70 % (w/w) and preferably ranges from about 55 % to about 60 % (w/w).

Lubricants and glidants can be employed in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants and glidants are hydrogenated vegetable oils, e.g hydrogenated Cottonseed oil, magnesium stearate, stearic acid, sodium lauryl sulfate, magnesium lauryl sulfate, colloidal silica, colloidal anhydrous silica talc, mixtures thereof, and others known in the art. Interesting lubricants are magnesium stearate, and mixtures of magnesium stearate with

colloidal silica. A preferred lubricant is magnesium stearate. A preferred glidant is colloidal anhydrous silica.

Glidants generally comprise 0.2 to 7.0 % of the total tablet weight, in particular 0.5 to 1.5%, more in particular 1 to 1.5% (w/w).

Lubricants generally comprise 0.2 to 7.0 % of the total tablet weight, in particular 0.2 to 1%, more in particular 0.5 to 1% (w/w).

Other excipients such as coloring agents and pigments may also be added to the formulations of the invention. Coloring agents and pigments include titanium dioxide and dyes suitable for food. A coloring agent is an optional ingredient in the formulation of the invention, but when used the coloring agent can be present in an amount up to 3.5 % based on the total tablet weight.

Flavors are optional in the formulation and may be chosen from synthetic flavor oils and flavoring aromatics or natural oils, extracts from plants leaves, flowers, fruits and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, bay oil, anise oil, eucalyptus, thyme oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth, The amount of flavor may depend on a number of factors including the organoleptic effect desired. Generally the flavor will be present in an amount from about 0 % to about 3 % (w/w).

As known in the art, tablet blends may be dry-granulated or wet-granulated before tabletting. The tabletting process itself is otherwise standard and readily practised by forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present invention may further be film-coated e.g. to improve taste, to provide ease of swallowing and an elegant appearance. Many suitable polymeric film-coating materials are known in the art. A preferred film-coating material is Opadry II 85F210036 Green. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, hydroxypropyl methylcellulose (HPMC), especially HPMC 2910 5 mPa.s, and acrylate-methacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain talc as an anti-adhesive. In tablets according to the invention, the film coat in

terms of weight preferably accounts for about 3 % (w/w) or less of the total tablet weight.

Preferred formulations are those wherein the weight of the particles or solid dispersions as described herein ranges from 20 to 40 %, in particular from 30 to 40 % of the total weight of the formulation.

The present invention further concerns a process of preparing solid dispersions as described herein, comprising blending ARN-509 and HPMCAS and extruding said blend at a temperature in the range from about 160°C to about 190 °C.

The present invention further concerns a process of preparing particles as described herein, comprising blending ARN-509 and HPMCAS, extruding said blend at a temperature in the range from about 160°C to about 190 °C, grinding the extrudate, and optionally sieving the particles.

Suitable extruders that may be used are the Haake mini-extruder, Leistritz 18 mm extruder, and the Leistritz 27 mm extruder.

The present invention further concerns a process of preparing particles or solid dispersions as described herein comprising mixing ARN-509 and HPMCAS in a suitable solvent and spray drying said mixture. In an aspect, the suitable solvent is a mixture of dichloromethane and methanol. In an aspect, the suitable solvent is a mixture of dichloromethane and methanol wherein the weight:weight ratio of dichloromethane to methanol in the mixture is 4 : 6 or 5:5, 4:6 being preferred.

A preferred crystalline form of ARN-509 for preparing the solid dispersions or particles as described herein is Form B, which is an anhydrous crystalline form (see hereinafter and reference is also made to WO2013/184681, which is incorporated herein by reference).

It is another object of the invention to provide a process of preparing a pharmaceutical formulation as described herein, in particular in the form of a tablet or a capsule, characterized by blending a therapeutically effective amount of a solid dispersion or particles as described herein, with a pharmaceutically acceptable carrier and compressing said blend into tablets or filling said blend in capsules.

Further, this invention concerns a solid dispersion or particles as described herein, for use in preparing a pharmaceutical formulation for administration, in particular oral administration, 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, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer.

The present invention also concerns the use of a solid dispersion or particles as described herein, for the preparation of a pharmaceutical formulation for administration, in particular oral administration, 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, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer.

The invention also relates to a method of treating an androgen receptor (AR)-related disease or condition, in particular cancer, more in particular prostate cancer, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer, in a mammal, in particular a human, which comprises administering, in particular orally, to said mammal, in particular human, an effective anticancer amount of a pharmaceutical formulation as described herein.

The invention further concerns the use of a pharmaceutical formulation as specified herein, for the manufacture of a medicament for treating an androgen receptor (AR)-related disease or condition, in particular cancer, more in particular prostate cancer, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer. Or, alternatively, the invention concerns a pharmaceutical formulation as specified herein for use in the treatment of an androgen receptor (AR)-related disease or condition, in particular cancer, more in

particular prostate cancer, including but not limited to castration-resistant prostate cancer, metastatic castration resistant prostate cancer, chemotherapy-naive metastatic castration resistant prostate cancer, biochemically relapsed hormone sensitive prostate cancer, or high-risk, non-metastatic castration-resistant prostate cancer.

The invention also relates to a pharmaceutical package suitable for commercial sale comprising a container, a pharmaceutical formulation as described herein, and associated with said package written matter.

The term "about" as used herein in connection with a numerical value is meant to have its usual meaning in the context of the numerical value. Where necessary the word "about" may be replaced by the numerical value ±10%, or ±5%, or ±2%, or ±1%. All documents cited herein are incorporated by reference in their entirety.

The following examples are intended to illustrate the present invention.

Example 1 : ARN-509 forms

For the preparation of different (crystalline) forms of ARN-509, reference is made to WO2013/184681, which is incorporated herein by reference. Different (crystalline or amorphous) forms of ARN-509 can be used to prepare the solid dispersions, particles or formulations according to the present invention.

A preferred form of ARN-509 for use in the preparation of the solid dispersions, particles or formulations according to the present invention is ARN-509 Form B, which is an anhydrous crystal. It was prepared by suspending ARN-509 Form A (reference is made to WO2013/184681, including for the diffraction data) in USP water and heating the slurry to 55±5 °C, holding at said temperature for at least 24 hours, followed by cooling the slurry to 25±5 °C. The resulting slurry was filtered, and the wet cake washed once with USP water. The wet cake was unloaded from the filter and dried under vacuum to afford ARN-509 Form B. Reference is also made to Example 2 below.

Solubility of Form A : 0.01 mg/ml in water.
Solubility of Form B : 0.004 mg/ml in water.

Example 2

Characterisation of ARN-509 Form B

Powder XRD

X-ray powder diffraction (XRPD) analyses were carried out on a PANalytical (Philips) X'PertPRO MPD diffractometer. The instrument is equipped with a Cu LFF X-ray tube.

The compound was spread on a zero background sample holder.

INSTRUMENT PARAMETERS

generator voltage:	45 kV
generator amperage:	40 mA
geometry:	Bragg-Brentano
stage:	spinner stage

MEASUREMENT CONDITIONS

scan mode:	continuous
scan range:	3 to 50° 2θ
step size:	0.02°/step
counting time:	30 sec/step
spinner revolution time:	1 sec
radiation type:	CuKα

Incident beam path		***Diffracted beam path***	
program. divergence slit:	15 mm	long anti scatter shield:	+
Soller slit:	0.04 rad	Soller slit:	0.04 rad
beam mask:	15 mm	Ni filter:	+
anti scatter slit:	1°	detector:	X'Celerator
beam knife:	+		

The X-ray powder diffraction pattern of ARN-509 Form B shows diffraction peaks without the presence of a halo, indicating that this compound is present as a crystalline product. The XRD pattern of ARN-509 Form B is shown in Figure 1.

Infrared spectrometry (Micro ATR-IR)

The samples were analyzed using a suitable microATR accessory.

apparatus:	Thermo Nexus 670 FTIR spectrometer
number of scans:	32
resolution:	1 cm^{-1}
wavelength range:	4000 to 400 cm^{-1}
detector:	DTGS with KBr windows
beamsplitter:	Ge on KBr
micro ATR accessory:	Harrick Split Pea with Si crystal

The spectrum of ARN-509 Form B is shown in Figure 2.

Differential scanning calorimetry (DSC)

The compound was transferred into a standard aluminum TA-Instrument sample pan. The sample pan was closed with the appropriate cover and the DSC curve was recorded on a TA-Instruments Q1000 MTDSC equipped with a RCS cooling unit, using the following parameters:

initial temperature:	25°C
heating rate:	10°C/min
final temperature:	250°C

The DSC curve of ARN-509 Form B shows the melting of the product at 194.9°C with a heat of fusion of 73J/g. See Figure 3.

Example 3.1 : Preparation of a solid dispersion of ARN-509:HPMCAS LG 1:3

ARN-509	2,500g
HPMC-AS LG	7,500g
Dichloromethane, [a]	76,000g
Methanol [a]	114,000g

[a] Removed during processing

The dichloromethane and methanol were transferred into a suitable container and stirring was started. Under continuous stirring ARN-509 Form B was added to the solvent mixture and stirred until dissolved. HPMCAS was added to the solution and stirred overnight. A yellowish viscous turbid mixture was obtained. The mixture was filtered inline through a GRID filter. The mixture was spray dried using a suitable spray dryer, e.g. Niro A/S PSD3 with a high pressure nozzle with the following

parameters : feed flow of 75 kg/hour, outlet temperature of 46 °C and a condenser temperature of -9 °C.

The spray dried product (SDP) was dried in a suitable dryer, e.g. tray dryer using vacuum, nitrogen flow and a drying temperature of 40 °C.

Example 3.2 : Preparation of tablets comprising a solid dispersion of ARN-509:HPMCAS 1:3

Spray dried powder (SDP) of Example 3.1	7,200g
Colloidal Anhydrous Silica	273g
Croscarmellose sodium	1,050g
Microcrystalline Cellulose	8,865g
Silicified Microcrystalline Cellulose	3,507g
Magnesium stearate [a]	105g

[a] Vegetable grade

for 30,000 tablets

The SDP was sieved and mixed with part (10/13) of the colloidal anhydrous silica to a homogeneous blend using a suitable blender. Part (1/2) of the croscarmellose sodium and the microcrystalline cellulose (all) were sieved and added to the blend and mixed using a suitable blender. A dry granulate was made by using a suitable compaction technique, e.g. roller compaction. The silicified microcrystalline cellulose, remainder of the croscarmellose sodium (1/2) and colloidal anhydrous silica (3/13) were sieved and added to the dry granulate and mixed using a suitable blender. The magnesium stearate was sieved, added to the blend and mixed using a suitable blender.

The blend was compressed into tablets (containing 60 mg of ARN 509) using a suitable tablet press.

Example 3.3 : Preparation of coated tablets

ARN-509 (60 mg) Tablets (see Example 3.2)	599.9g
Opadry II 85F210036 Green	17.997g
Purified Water [a]	71.988g

[a] Removed during processing

per batch of 857 tablets

The purified water was transferred into a suitable container. The coating powder was added and mixed with a suitable mixer. The core tablets were film coated with the coating suspension using a suitable coater.

Example 4.1 : Preparation of a solid dispersion of ARN-509:HPMCAS LF 1:2

ARN-509	333.33 mg
HPMCAS LF	666.67 mg
Acetone [a]	19000 mg

[a] Removed during processing

(the reported amounts are for 1 g of SDP (spray dried product))

The acetone was transferred into a suitable container, and HPMCAS and ARN-509 Form B were added. After mixing the ingredients using a suitable mixer, the mixture was spray dried using a suitable spray dryer, e.g. Buchi mini spray dryer with the following parameters : spray rate in the range from 6.2-6.7 gram/minute, outlet temperature in the range from 46 °C -49 °C and a condenser temperature in the range from -18 °C to -21 °C.

The spray dried product (SDP) was dried in a suitable dryer, e.g. tray dryer using vacuum, nitrogen flow and a drying temperature of 40 °C.

Example 4.2 : Preparation of tablets comprising a solid dispersion of ARN-509:HPMCAS 1:2

Spray dried powder of 4.1 (SDP)	360.0 mg
Colloidal Anhydrous Silica	18.2 mg
Croscarmellose sodium	70.0 mg
Silicified Microcrystalline Cellulose	944.8 mg
Magnesium stearate	7.0 mg

(amounts for 1 tablet)

The SDP, part (7110/9448) of the silicified microcrystalline cellulose, part (10/13) of the colloidal anhydrous silica and part (1/2) of the croscarmellose sodium were sieved and mixed to a homogenous blend using a suitable blender. A dry granulate was made by using a suitable compaction technique. The remainder of the silicified microcrystalline cellulose (2338/9448), colloidal anhydrous silica (3/13) and croscarmellose sodium (1/2) were sieved and added to the dry granulate and further mixed using a suitable blender. Magnesium stearate was sieved and added to the blend and mixed further using a suitable blender. The blend was compressed into tablets using a suitable tablet press.

Example 5.1 : Preparation of a solid dispersion of ARN-509:HPMCAS LF 1:3 by hot melt extrusion (HME)

ARN-509	250 mg
HPMCAS LF	750 mg

(the reported amounts are for 1 g of HME product)

The HPMCAS and ARN-509 Form B were blended in a suitable recipient using a suitable blender. Hot melt extrusion was performed in a Haake extruder, flush mode, maximum temperature 180 ^{0}C, screw speed 50 rpm. The hot melt extrudate was collected and milled in a suitable mill. The milled hot melt extrudate was sieved using a suitable sieve (250 μm).

Example 5.2 : Preparation of tablets comprising a solid dispersion of ARN-509:HPMCAS LF 1:3 (HME)

HME powder of 5.1	240.0 mg
Colloidal Anhydrous Silica	9.1 mg
Croscarmellose sodium	35.0 mg
Silicified Microcrystalline Cellulose	412.4 mg
Magnesium stearate	3.5 mg

(amounts for 1 tablet)

HME powder of 5.1	480.0 mg
Colloidal Anhydrous Silica	18.2 mg
Croscarmellose sodium	70.0 mg
Silicified Microcrystalline Cellulose	824.8 mg
Magnesium stearate	7.0 mg

(amounts for 1 tablet)

The silicified microcrystalline cellulose, croscarmellose sodium and colloidal anhydrous silica were sieved and mixed with the hot melt extrudate to a homogenous blend using a suitable blender. Magnesium stearate was sieved and added to the blend and mixed further using a suitable blender. The blend was compressed into tablets using an eccentric tableting press.

Example 6.1 : Preparation of a solid dispersion of ARN-509:HPMCAS LF 1:3 SDP

ARN-509	250.0 mg

HPMCAS LF	750.0 mg
Acetone [a]	19000.0 mg

[a] Removed during processing

(the reported amounts are for 1 g of SDP (spray dried product))

The acetone was transferred into a suitable container and HPMCAS LF and ARN-509 Form B were added. After mixing the ingredients using a suitable mixer, the mixture was spray dried using a suitable spray dryer, e.g. Buchi mini spray dryer with the following parameters : spray rate in the range from 5.9-6.6 gram/minute, outlet temperature in the range from 46 °C - 49 °C and a condenser temperature in the range from -15 °C to -21 °C.

The spray dried product (SDP) was dried in a suitable dryer, e.g. tray dryer using vacuum, nitrogen flow and a drying temperature of 40 °C.

Example 6.2 : Preparation of tablets comprising a solid dispersion of ARN-509: HPMCAS 1:3

Spray dried powder of 6.1 (SDP)	240.0 mg
Colloidal Anhydrous Silica	9.1 mg
Croscarmellose sodium	35.0 mg
Silicified Microcrystalline Cellulose	412.4 mg
Magnesium stearate	3.5 mg

(amounts for 1 tablet)

Spray dried powder of 6.1 (SDP)	480.0 mg
Colloidal Anhydrous Silica	18.2 mg
Croscarmellose sodium	70.0 mg
Silicified Microcrystalline Cellulose	824.8 mg
Magnesium stearate	7.0 mg

(amounts for 1 tablet)

The SDP, part (2955/4124) of the silicified microcrystalline cellulose, part (10/13) of the colloidal anhydrous silica and part (1/2) of the croscarmellose sodium were sieved and mixed to a homogenous blend using a suitable blender. A dry granulate was made by using a suitable compaction technique. The remainder of the silicified microcrystalline cellulose (1169/4124), colloidal anhydrous silica (3/13) and croscarmellose sodium (1/2) were sieved and added to the dry granulate and further mixed using a suitable blender. Magnesium stearate was sieved and added to the blend

and mixed further using a suitable blender. The blend was compressed into tablets using an eccentric tabletting press.

Bioavailability study

Test system

Species: Marshall beagle dogs

Supplier: Marshall Farms, Italy/USA

Gender and age: male (n = 12), approximately 1-7 years

Body weights: 8-13 kg at the start of the experimental phase

Diet and water supply:

Continuous access to water

Dosing : fasted for about 21 hours before dosing till ± 2 hours after dosing. Afterwards, dogs had free access to food until the late afternoon.

Test compound and formulations

Formulation 1: 60 mg tablet containing ARN-509-HPMC AS-LF ratio 1/3 SDP

Formulation 2: 60 mg tablet containing ARN-509-HPMC AS-LF ratio 1/3 HME

Formulation 3: a nonaqueous, lipid-based solution filled into softgel capsules, each containing 30 mg ARN-509

Blood sampling and plasma preparation

Blood samples (2 ml on EDTA) were taken from a jugular vein. Within 1 hour of sampling, the blood samples were centrifuged and within 2 hours after the start of centrifugation, plasma was stored in the freezer.

Dose administration

Day of Dosing	Formulation	Route	Dose (mg/dog)	Tablet (pcs)	Dog Nos.
Day 0	**Formulation 1**	PO (gavage)	60	1	n=4
	Formulation 2	PO (gavage)	60	1	n=4
	Formulation 3	PO (gavage)	60	2	n=4

Bioanalysis

All study samples were analyzed using a qualified LC-MS/MS method. The samples were subjected to a selective sample cleanup, followed by HPLC-MS/MS.
HPLC separation was done using non-chiral reversed phase liquid chromatography. Subsequent MS/MS analysis was performed using triple quadrupole mass spectrometry in the Multiple Reaction Monitoring (MRM) mode, optimized for the compound. Samples were quantified against calibration curves prepared to cover the concentration range of the study samples. The curves were prepared in the same matrix as the study samples. For each analytical batch, independent quality control samples, prepared in the same matrix as the samples, were analyzed together with the study samples and calibration curve. All analytical batches were accepted based on calibration curve and QC acceptance criteria in line with the current FDA guidelines.

Data analysis

Individual plasma concentration-time profiles were subjected to a pharmacokinetic analysis using validated Phoenix software. A non-compartmental analysis using the linear up/log down trapezoidal rule was used for all data.

Results

The mean C_{max}, T_{max}, AUC and F_{rel} values of ARN-509 in male beagle dogs after single oral administration of the 3 formulations are presented below:

Formulation	**1**	**2**	**3**
C_{max} (ng/ml)	3900	2630	4110
T_{max} (h)	0.5-1	1-2	1-2
AUC_{last} (ng.h/ml) [1)]	183000	159000	157000
AUC_{0-inf} (ng.h/ml)	183000	151000[2)]	167000
Frel (AUC_{last} ratios)	117%	101%	

[1)] T_{last} in majority of animals was 168h; [2)] n=3

Formulation 1: HPMC AS-LF ratio 1/3 (SDP)
Formulation 2: HPMC AS-LF ratio 1/3 (HME)
Formulation 3: softgel reference capsule

Stability tests performed on powders of Example 3.1 and 5.1

The tests were performed on the powders packed in LDPE/Alu bags.

1.Appearance testing

A visual examination was performed on the powder of Example 3.1 and Example 5.1 stored under different storage conditions as indicated in table a1 and a2 below.

The results are reported in the table a1 and a2 below.

2.Water content

The water content was determined by means of a vaporized coulometric Karl Fischer determination in accordance with USP/Ph. Eur.

Powder of Example 3.1 or Example 5.1 was stored as indicated in table a1 or a2 below.

About 50.00 mg (±5.00 mg) of the sample was weighted accurately into a vial and the vial was crimped securely.

The results are reported in table a1 and a2 below.

The following instrumentation, reagents and solutions and parameters were used.

INSTRUMENTATION

Coulometer: 831 KF Coulometer Metrohm
Oven: 774 Sample Oven Processor Metrohm
Generator electrode: Electrode with diapraghm Metrohm 6.0344.100
Indicator electrode: Double Pt-wire electrode Metrohm 6.0341.100

REAGENTS AND SOLUTIONS

Anode solution: Hydranal Coulomat AG Oven (Fluka 34739)
Cathode solution: Hydranal Coulomat CG (Fluka 34840)
Water standard: Hydranal Water Standard 1.00 (Fluka 34828)

Oven Parameters

Carrier gas : N_2
Flow rate : Setpoint 60 mL/min
Read out value minimum 20 mL/min

Oven temperature : 120^{0}C

Coulometer Parameters

Titration Parameters

Extr. time : 60 s

Drift correction : Auto

Start Conditions

Pause : 60 s

Start drift : maximum 12 µg/min

Time cond. OK : 10 s

Stop Parameters

Rel. drift : 5 µg/min

Alternative coulometer parameters may be used provided system suitability requirements are met

3. pXRD testing for the detection of crystalline ARN-509

The physical stability of powder of Example 3.1 and Example 5.1 stored under different storage conditions was followed up using powder X-Ray diffraction. The XRD pattern of the powder was compared to the XRD pattern of the corresponding powder measured at time zero (amorphous product).

The powder was brought on to the zero background sample holder. A X-ray measurement of the sample was performed.

The results are reported in table a1 and a2 below.

The following instrumentation and parameters were used.

INSTRUMENTATION

Pananalytical X'Pert PRO MPD diffractometer PW3050/60

X-ray tube Cu LFF PW3373/10

Detector: X'Celerator

Sample stage: spinner

Sample holder: zero background sample holder

Instrument settings

Spinner revolution time: 1 rps

Generator voltage: 45 kV

Generator current: 40 mA

Optical components in X-ray beam path

Incident beam path:

Programmable divergence slit: irradiated length 15 mm

Soller slit: 0.04 rad

Beam mask: 15 mm

Anti-scatter slit: 1°

Beam knife +

Diffracted beam path:

Programmable Anti-scatter slit: 1°

Soller slit: 0.04 rad

Filter: Ni

INSTRUMENT PARAMETERS

Geometry: Bragg-Brentano

Radiation: CuKα

Step size: 0.02°

Scan range: from 3° 2θ to 50° 2θ

Counting time per step:60 sec

Table a1: Test conditions and results for powders of Example 3.1 stored in LDPE/Alu Bags –appearance and water content and crystallinity results

Parameter		Appearance [a]	Water content (%)	Crystallinity
Storage condition	Storage time (months)	Visual examination		
	Initial	Pass	0.6	Amorphous product
30°C/75%RH	6	Pass	1.0	Amorphous product
	9	Pass	1.0	Amorphous product
	12	Pass	1.7	Amorphous product

[a] Pass : White to light yellow, fine to granular powder

Table a2: Test conditions and results for powders of Example 5.1 stored in LDPE/Alu Bags –appearance and water content and crystallinity results

Parameter		Appearance [a]	Water content (%)	Crystallinity
Storage condition	Storage time (months)	Visual examination		
	Initial	Pass	2.3	Amorphous product
30°C/75%RH	6	Pass	2.0	Amorphous product

[a] Pass : White to light yellow-brownish, fine to granular powder

For the appearance, no substantial stability related changes were observed during storage of the drug product intermediate powder at the different storage conditions.

For the water content, no substantial stability related changes were observed during storage of the drug product intermediate powder at the different storage conditions.

For the crystallinity, no substantial stability related changes were observed during storage of the drug product at the different storage conditions.

4. Assay of ARN-509-chromatographic purity

The concentration of ARN-509 and its degradation products in powders of Example 3.1 and Example 5.1 stored under different storage conditions were determined by gradient Reversed-Phase UHPLC with UV Detection.

Powders were stored as indicated in table b1 and b2 below.

Approximately 240.00 mg powder was weighted accurately into a 250-mL volumetric flask. Approximately 125 mL acetonitrile was added by graduated cylinder and the whole was shaken mechanically for 30 minutes and diluted to volume with water till approximately 1 cm under the marker. The whole was shaked up manually vigorously. The sample solution was allowed to equilibrate to ambient temperature and was diluted to volume with water. Just before filtering, the volumetric flask was shaked up manually vigorously. The sample solution was filtered through a chemical resistant 0.2 µm filter. The first 3 mL filtrate were discarded into a waste container, not back into the volumetric flask.

The sample solution is stable for 4 days, if stored in refrigerator, protected from light (closed cabinet).

The results are reported in table b1 and b2 below.

The following solutions and instrumentation and parameters were used.

Mobile Phases

Mobile Phase A

10 mM NH_4Ac + 0.1% TFA / Acetonitrile (90/10, v/v).

Mobile Phase B

Acetonitrile

UHPLC Conditions for Identification, Assay and Chromatographic Purity

Column: Acquity BEH C18, 150 mm length × 2.1 mm i.d., 1.7 µm particle size

Column Temperature: 45 ^{0}C

Auto-Sampler Temperature: 5 ^{0}C

Flow Rate: 0.40 mL/min

Detection: UV

Wavelength: 268 nm

Injection Volume: 3 µL

Data Collection Time: 35 minutes

Analysis Run Time: 40 minutes

A linear gradient was programmed as demonstrated in the below table.

Linear Gradient Program

Time (min)	A (% vol)	B (% vol)
0	100	0
35	30	70
36	100	0
40	100	0

Table b1: Test conditions and results for powders of Example 3.1 stored in LDPE/Alu Bags–assay and degradation products results

Parameter		Assay(%)	Degradation products (%)
Storage condition	Storage time (months)	ARN-509	Total degradation products (sum of all degradation products ≥0.05% (totals are calculated on unrounded results)
	Initial	99.3	0.066
30°C/75%RH	6	98.9	0.11
	9	98.0	0.07
	12	98.2	0.06

Table b2: Test conditions and results for powders of Example 5.1 stored in LDPE/Alu Bags–assay and degradation products results

Parameter		Assay(%)	Degradation products (%)
Storage condition	Storage time (months)	ARN-509	Total degradation products (sum of all degradation products ≥0.05% (totals are calculated on unrounded results)
	Initial	96.4	0.11
30°C/75%RH	6	96.3	0.08

No substantial stability related changes were observed during storage of the drug product intermediate powders at the different storage conditions.

5. Water activity

The water activity was determined with a Novasina a_w-meter.

The test was performed on powders of Example 3.1 and Example 5.1.

The results are reported in table c1 and c2 below.

Table c1: Test conditions and results for powders of Example 3.1 stored in LDPE/Alu Bags –Water activity results

Parameter		Water activity
Storage condition	Storage time (months)	
	Initial	0.21
30°C/75%RH	12	0.38

Table c2: Test conditions and results for powders of Example 5.1 stored in LDPE/Alu Bags –Water activity results

Parameter		Water activity
Storage condition	Storage time (months)	
	Initial	0.44

Stability tests performed on tablets of Example 3.3

Tests were performed on tablets stored in HDPE Bottles with Desiccant (silica gel).

1.Appearance testing

A visual examination was performed on the tablets of Example 3.3 stored under different storage conditions as indicated in table 1 below.

The results are reported in table 1 below.

2.Water content

The water content was determined by means of a vaporized coulometric Karl Fischer determination in accordance with USP/Ph. Eur.

Tablets of Example 3.3 were stored as indicated in table 1 below.

Tablets were grinded using a Retsch Mixer Mill. Immediately after grinding, about 50.00 mg (±5.00 mg) of the sample was weighted accurately into a vial and the vial was crimped securely.

The results are reported in table 1 below.

The following instrumentation, reagents and solutions and parameters were used.

INSTRUMENTATION

Coulometer: 831 KF Coulometer Metrohm

Oven: 774 Sample Oven Processor Metrohm

Generator electrode: Electrode with diapraghm Metrohm 6.0344.100

Indicator electrode: Double Pt-wire electrode Metrohm 6.0341.100

REAGENTS AND SOLUTIONS

Anode solution: Hydranal Coulomat AG Oven (Fluka 34739)

Cathode solution: Hydranal Coulomat CG (Fluka 34840)

Water standard: Hydranal Water Standard 1.00 (Fluka 34828)

Oven Parameters

Carrier gas : N_2

Flow rate : Setpoint 60 mL/min

Read out value minimum 20 mL/min

Oven temperature : 120^0C

Coulometer Parameters

Titration Parameters

Extr. time : 60 s

Drift correction : Auto

Start Conditions

Pause : 60 s

Start drift : maximum 12 µg/min

Time cond. OK : 10 s

Stop Parameters

Rel. drift : 5 µg/min

Alternative coulometer parameters may be used provided system suitability requirements are met

Table 1: Test conditions and results for tablets of Example 3.3 stored in HDPE Bottles with Desiccant (silica gel) –appearance and water content results

Parameter		Appearance [a]	Water content (%)
Storage condition	Storage time (months)	Visual examination	
	Initial	Pass	3.8
-20°C	1	Pass	2.4
5°C	3	Pass	2.9
	6	Pass	2.2
	12	Pass	3.2
25°C/60%RH	6	Pass	2.4
	12	Pass	3.7
30°C/75%RH	1	Pass	2.4
	3	Pass	3.0
	6	Pass	2.5
	9	Pass	3.2
	12	Pass	3.7
40°C/75%RH	1	Pass	2.5
	3	Pass	3.3
	6	Pass	3.2
50°C	1	Pass	2.2
	3	Pass	2.9
Light ICH		Pass	2.3

[a] Pass : Greenish colored, oblong tablet

Light ICH: integrated near UV energy not less than 200 W·h/m^2, overall illumination not less than 1200 klux·h

For the appearance, no substantial stability related changes were observed during storage of the drug product at the different storage conditions.

A slight increase in water content was observed.

3. pXRD testing for the detection of crystalline ARN-509

The physical stability of different tablets of Example 3.3 stored under different storage conditions was followed up using powder X-Ray diffraction. The XRD pattern of the tablets was compared to the XRD pattern of the corresponding tablets at time zero (amorphous product).

One tablet was gently grinded to a fine powder using a mortar and pestle. The powder was loaded into the 16 mm sample holder using the back loading technique. A X-ray measurement of the sample was performed.

The results are reported in table 2 below.

The following instrumentation and parameters were used.

INSTRUMENTATION

Philips X'Pert PRO MPD diffractometer PW3050/60
X-ray tube Cu LFF PW3373/10
Detector: X'Celerator
Sample stage: spinner
Sample holder: cavity diameter 16 mm, cavity depth 2.5 mm

Instrument settings

Spinner revolution time: 1 rps
Generator voltage: 45 kV
Generator current: 40 mA

Optical components in X-ray beam path

Incident beam path:

Programmable divergence slit: irradiated length 10 mm
Soller slit: 0.04 rad
Beam mask: 10 mm
Anti-scatter slit: 1°
Beam knife +

Diffracted beam path:

Programmable Anti-scatter slit: 1°
Soller slit: 0.04 rad
Filter: Ni

INSTRUMENT PARAMETERS

Geometry: Bragg-Brentano
Radiation: CuKα
Step size: 0.02°
Scan range: from 3° 2θ to 50° 2θ

Counting time per step:100 sec

Table 2: Test conditions and results for tablets of Example 3.3 stored in HDPE Bottles with Desiccant (silica gel)–crystallinity results

Parameter		Crystallinity
Storage condition	Storage time (months)	
	Initial	Amorphous drug substance in drug product
-20°C	1	Amorphous drug substance in drug product
5°C	3	Amorphous drug substance in drug product
	6	Amorphous drug substance in drug product
	12	Amorphous drug substance in drug product
25°C/60%RH	6	Amorphous drug substance in drug product
	12	Amorphous drug substance in drug product
30°C/75%RH	1	Amorphous drug substance in drug product
	3	Amorphous drug substance in drug product
	6	Amorphous drug substance in drug product
	9	Not Tested
	12	Amorphous drug substance in drug product
40°C/75%RH	1	Amorphous drug substance in drug product
	3	Amorphous drug substance in drug product
	6	Amorphous drug substance in drug product
50°C	1	Amorphous drug substance in drug product
	3	Amorphous drug substance in drug product
Light ICH		Amorphous drug substance in drug product

Light ICH: integrated near UV energy not less than 200 W·h/m^2, overall illumination not less than 1200 klux·h

No substantial stability related changes were observed during storage of the drug product at the different storage conditions.

4. Assay of ARN-509-chromatographic purity

The concentration of ARN-509 and its degradation products in tablets of Example 3.3 stored under different storage conditions were determined by gradient Reversed-Phase UHPLC with UV Detection.

Tablets were stored as indicated in table 3 below.

Five tablets were weighted accurately. Mean tablet weight was determined. Tablets were grinded to a fine powder. An amount of homogenized powder equivalent to the mean tablet weight was accurately weighted into a 250-mL volumetric flask. Approximately 125 mL acetonitrile was added by graduated cylinder and the whole was shaken mechanically for 30 minutes and diluted to volume with water till approximately 1 cm under the marker. The whole was shaked up manually vigorously. The sample solution was allowed to equilibrate to ambient temperature and was diluted to volume with water. Just before filtering, the volumetric flask was shaked up manually vigorously. The sample solution was filtered through a chemical resistant 0.45 µm filter. The first 3 mL filtrate was discarded into a waste container, not back into the volumetric flask.

The sample solution is stable for 4 days, if stored in refrigerator, protected from light (closed cabinet).

The results are reported in table 3 below.

The following solutions and instrumentation and parameters were used.

Mobile Phases

Mobile Phase A

10 mM NH_4Ac (aqueous ammonium acetate) + 0.1% TFA (trifluoroacetic acid) / Acetonitrile (90/10, v/v).

Mobile Phase B

Acetonitrile

UHPLC Conditions for Identification, Assay and Chromatographic Purity

Column: Acquity BEH C18, 150 mm length × 2.1 mm i.d., 1.7 µm particle size

Column Temperature: 45 ^{0}C

Auto-Sampler Temperature: 5 ^{0}C

Flow Rate: 0.40 mL/min

Detection: UV

Wavelength: 268 nm

Injection Volume: 3 µL

Data Collection Time: 35 minutes

Analysis Run Time: 40 minutes

A linear gradient was programmed as demonstrated in the below table.

Linear Gradient Program

Time (min)	A (% vol)	B (% vol)
0	100	0
35	30	70
36	100	0
40	100	0

Table 3: Test conditions and results for tablets of Example 3.3 stored in HDPE Bottles with Desiccant (silica gel)–assay and degradation products results

Parameter		Assay(%)	Degradation products (%)
Storage condition	Storage time (months)	ARN-509	Total degradation products (sum of all degradation products ≥0.05% (totals are calculated on unrounded results)
	Initial	102.3	0.11
-20°C	1	97.7	0.06
5°C	3	100.5	0.12
	6	99.7	0.07
	12	98.6	0.07
25°C/60%RH	6	100.5	0.07
	12	101.3	0.11
30°C/75%RH	1	98.8	0.11
	3	98.7	0.12
	6	100.4	0.07
	9	100.1	0.11
	12	99.5	0.07
40°C/75%RH	1	96.2	0.06
	3	98.5	0.12
	6	101.4	0.12
50°C	1	100.1	0.11
	3	100.6	0.07
Light ICH		97.5	0.07

Light ICH: integrated near UV energy not less than 200 W·h/m^2, overall illumination not less than 1200 klux·h

No substantial stability related changes were observed during storage of the drug product at the different storage conditions.

5.Dissolution

The dissolution test was performed using Paddle Apparatus (USP type 2, Ph.Eur., JP.) at 75 rpm in 900 mL of 0.5% (w/v) cetyltrimethylammonium bromide (CTAB) in 0.05 M sodium phosphate buffer pH 4.5.

Samples were taken by Distek® sample needles with solid housing and samples were filtered with Whatman®Spartan® 0.45 μm RC (regenerated cellulose) membrane 30 mm diameter filters.

The determination of the quantity of ARN-509 present in the dissolution samples was based upon an isocratic ultra high performance liquid chromatographic (UHPLC) method with UV detection.

The test was performed on tablets of Example 3.3 stored under different storage conditions as indicated in table 4 below.

The following instrumentation, reagents and solutions and parameters were used.

INSTRUMENTATION

Dissolution Instrument: Paddle apparatus (USP type 2, Ph. Eur., JP).

UHPLC Instrument: Waters Acquity H-Class with UV detector.

Data Acquisition System: Waters Empower.

Analytical Balance: Sensitive to 0.01 g.

Analytical Balance: Sensitive to 0.01 mg.

pH Meter: Sensitive to 0.01 pH units.

Thermometer: Sensitive to 0.1 ^{0}C.

REAGENTS AND SOLUTIONS

Reagents

Cetrimonium bromide,cetyltrimethylammonium bromide, hexadecyltrimethylammonium bromide,(CTAB): Pro Analysis, 99.0% Purity.

Sodium phosphate monobasic monohydrate ($NaH_2PO_4.H_2O$): ACS Grade.

Trifluoroacetic acid: HPLC Grade, 99.0% Purity.

Acetonitrile: HPLC Grade.

Mobile Phase

Mobile Phase A: 0.1% (v/v) TFA in water

Mobile Phase B: Acetonitrile

PROCEDURE

Dissolution Parameters

Apparatus: Paddle Apparatus (USP type 2, Ph.Eur, JP.).

Vessels: 1-L glass.

Rotation Speed: 75 rpm.

Dissolution Medium: 0.5% (w/v) CTAB in 0.05 M Phosphate Buffer pH 4.5.

Volume of Medium: 900 mL.

Medium Degassing: Not Required.

Medium Replacement: Not Required.

Temperature: 37.0 ±0.5 ^{0}C.

Sinker: Use no sinker.

Sample Introduction: Transfer 1 tablet into each dissolution vessel.

Analytical Finish - UHPLC Parameters

Conditions

Column: Acquity UHPLC® CSH C18 1.7-µm particle size, 2.1 ×50 mm i.d.

Column Temperature: 60 ± 5 ^{0}C.

Sample Temperature: Ambient.

Flow Rate: 0.6 mL/min.

Detection: UV at 242 nm.

Injection Volume: 3 µL.

Elution Mode: Isocratic.

Mobile Phase: 50/50 (v:v), 0.1% TFA in water : Acetonitrile.

Degas using suitable means.

Run Time (guide): 1.5 minutes.

Retention Time (guide): Approximately 0.7 minutes for ARN-509

Wash Solvent: Acetonitrile.

Needle Wash : Acetonitrile.

Seal Wash Solvent : 90/10 (v:v), Water:Acetonitrile.

Purge Solvent: 90/10 (v:v), Water:Acetonitrile.

Sampling Rate: 20 points/sec with filter constant normal.

Table 4: Test conditions and results for tablets of Example 3.3 stored in HDPE Bottles with Desiccant (silica gel)–Dissolution results

Parameter		Dissolution mean (%)(min-max)						
Storage condition	Storage time (months)	5 min	10 min	15 min	20 min	30 min	45 min	60 min
	Initial	65 (64-65)	87 (86-88)	94 (93-96)	97 (96-100)	99 (97-102)	100 (97-102)	100 (98-103)
-20°C	1	64 (63-66)	85 (84-87)	92 (91-93)	95 (94-97)	97 (95-99)	97 (95-99)	97 (95-100)
5°C	3	65 (63-66)	87 (85-88)	94 (92-96)	97 (95-99)	99 (97-101)	99 (97-101)	99 (97-101)
	6	63 (61-64)	84 (83-86)	92 (91-94)	95 (93-97)	96 (94-100)	97 (95-100)	97 (95-100)
	12	60 (57-62)	83 (82-84)	90 (89-93)	93 (92-96)	95 (93-98)	95 (93-99)	95 (93-99)
25°C/ 60%RH	6	68 (67-70)	84 (83-86)	92 (90-93)	95 (93-96)	97 (94-99)	97 (95-99)	97 (95-99)
	12	63 (62-65)	85 (84-86)	93 (92-94)	96 (95-98)	98 (97-99)	99 (97-100)	99 (97-100)
30°C/ 75%RH	1	63 (60-64)	85 (84-86)	93 (91-94)	96 (94-97)	98 (95-99)	98 (95-100)	98 (96-100)
	3	65 (64-66)	86 (85-86)	94 (93-95)	97 (96-98)	99 (97-100)	99 (98-100)	99 (98-100)
	6	64 (63-67)	86 (85-87)	94 (93-94)	97 (95-98)	99 (97-100)	99 (97-101)	99 (97-101)
	9	62 (61-64)	85 (84-86)	92 (91-93)	95 (94-97)	98 (95-99)	98 (96-99)	98 (96-99)
	12	65 (62-66)	86 (85-87)	93 (92-94)	96 (93-98)	97 (95-100)	98 (95-100)	98 (95-100)
40°C/ 75%RH	1	63 (62-65)	86 (84-87)	93 (91-94)	96 (93-98)	99 (94-101)	99 (94-102)	99 (95-101)
	3	65 (64-67)	86 (85-87)	93 (92-96)	96 (95-99)	98 (96-101)	99 (97-102)	99 (97-101)

Parameter		Dissolution mean (%)(min-max)						
Storage condition	Storage time (months)	5 min	10 min	15 min	20 min	30 min	45 min	60 min
	6	66 (65-67)	86 (85-88)	93 (92-95)	96 (94-98)	97 (95-100)	97 (96-100)	97 (96-101)
50°C	1	64 (63-64)	86 (84-87)	94 (92-96)	97 (95-99)	99 (97-101)	100 (97-102)	100 (98-103)
	3	65 (64-65)	86 (85-87)	94 (93-96)	97 (95-100)	99 (97-102)	100 (97-103)	100 (97-103)
Light ICH		64 (63-65)	85 (85-86)	93 (92-94)	96 (95-97)	98 (97-99)	98 (96-99)	98 (97-99)

Light ICH: integrated near UV energy not less than 200 W·h/m^2, overall illumination not less than 1200 klux·h

No substantial stability related changes were observed during storage of the drug product at the different storage conditions.

6. Water activity

The water activity was determined with a Novasina a_w-meter.

The test was performed on tablets of Example 3.3.

The results are reported in table 5 below.

Table 5: Test conditions and results for tablets of Example 3.3 stored in HDPE Bottles with Desiccant (silica gel)–Water activity results

Parameter		Water activity
Storage condition	Storage time (months)	
	Initial	0.50
5°C	12	0.14
25°C/60%RH	12	0.22
30°C/75%RH	12	0.27

A slight decrease in water activity was observed after 12 months storage at the tested conditions.

7. Microbiological purity

The microbiological purity of the tablets of Example 3.3 was tested according to USP <61> and <62>, and Ph.Eur.2.6.12 and 2.6.13.

Results are reported in table 6 below.

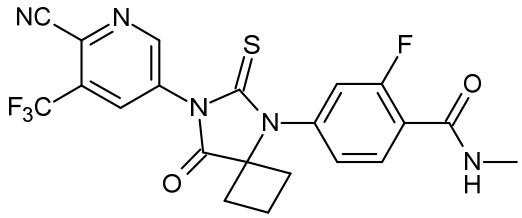
Table 6: Test conditions and results for tablets of Example 3.3 stored in HDPE Bottles with Desiccant (silica gel)–Microbiological Purity Results

Parameter		Total Aerobic Microbial count (cfu/g)	Total combined Molds and Yeasts Count (cfu/g)	Pathogens : E.Coli
Storage condition	Storage time (months)	USP <61>/ Ph.Eur.2.6.12	USP <61>/ Ph.Eur.2.6.12	USP <62>/ Ph.Eur.2.6.13
	Initial	<50	<50	Absent in 1g
5°C	12	<50	<50	Absent in 1g
25°C/60%RH	12	<50	<50	Absent in 1g
30°C/75%RH	12	<50	<50	Absent in 1g

No substantial stability related changes were observed during storage of the drug product at the different storage conditions.

It is within the knowledge of the skilled person to recognize equivalent conditions, solutions, reagents, parameters and instrumentation to the ones described above. It is within the knowledge of the skilled person to recognize appropriate reference solutions, calculation methods, suitability tests.

Claims



1. A solid dispersion comprising (ARN-509) and hydroxypropyl methylcellulose acetate succinate (HPMCAS).

2. The solid dispersion according to claim 1 wherein the dispersion consists of ARN-509 and HPMCAS.

3. The solid dispersion according to claim 1 or 2 wherein the weight-by-weight ratio of ARN-509 : HPMCAS in the solid dispersion is in the range from 1 : 1 to 1 : 5.

4. The solid dispersion according to claim 3 wherein the weight-by-weight ratio of ARN-509 : HPMCAS in the solid dispersion is 1:3.

5. The solid dispersion according to claim 3 wherein the weight-by-weight ratio of ARN-509 : HPMCAS in the solid dispersion is 1:2.

6. The solid dispersion according to claim 3 wherein the weight-by-weight ratio of ARN-509 : HPMCAS in the solid dispersion is 1:1.

7. The solid dispersion according to any one of the preceding claims wherein ARN-509 is present in amorphous form.

8. The solid dispersion according to any one of the preceding claims wherein the dispersion is a solid solution.

9. The solid dispersion according to any one of the preceding claims wherein the HPMCAS is HPMCAS granular grade.

10. The solid dispersion according to any one of the preceding claims obtainable by spray drying.

11. The solid dispersion according to any one of claims 1 to 9 obtainable by hot melt extrusion.

12. A particle consisting of a solid dispersion as defined in any one of the preceding claims.

13. A particle comprising a solid dispersion as defined in any one of claims 1 to 11.

14. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a solid dispersion according to any one of claims 1 to 11.

15. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and particles according to claim 12 or 13.

16. The formulation according to claim 14 or 15 wherein the formulation comprises 60 mg of ARN-509.

17. The formulation according to claim 14 or 15 wherein the formulation comprises 120 mg of ARN-509.

18. The formulation according to claim 14 or 15 wherein the formulation comprises 240 mg of ARN-509.

19. The formulation according to any one of claims 14 to 18 wherein the weight of the solid dispersion ranges from 20 to 40 % of the total weight of the formulation.

20. The formulation according to any one of claims 14 to 19 wherein the formulation is a tablet.

21. The formulation according to claim 20 which is suitable for oral administration.

22. A process for preparing the solid dispersion according to claim 10 comprising the steps of mixing ARN-509 and HPMCAS in a suitable solvent and spray drying said mixture.

23. The process according to claim 22 wherein the suitable solvent is a mixture of dichloromethane and methanol.

24. The process according to claim 23 wherein the weight:weight ratio of dichloromethane to methanol in the mixture is 4 : 6.

25. Use of the pharmaceutical formulation according to any one of claims 14 to 21 for the preparation of a medicament for the treatment of prostate cancer.

26. Use according to claim 25 wherein the medicament is for oral administration.

27. A combination of a pharmaceutical formulation according to any one of claims 14 to 21 and another anticancer agent.

28. The combination according to claim 27 wherein the other anticancer agent is an androgen biosynthesis inhibitor.

29. The combination according to claim 27 wherein the other anticancer agent is abiraterone acetate.

30. The combination according to any one of claims 27 to 29 further comprising prednisone.