

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Application No. 63/578,566 filed August 24, 2023, which is hereby incorporated by reference herein in its entirety.

FIELD

[0002] This disclosure relates to fixed dose combinations comprising azacitidine, or a pharmaceutically acceptable salt thereof, and cedazuridine, or a pharmaceutically acceptable salt thereof.

BACKGROUND

[0003] Cancer is a worldwide health problem; the World Health Organization estimates that cancer accounted for nearly 10 million deaths worldwide in 2020. Every cancer type requires a specific treatment regimen and sometimes cancers acquire resistance to certain treatments. Combination therapies can reduce development of resistance and improve overall survival (OS) and/or delay disease progression (progression free survival (PFS)).

[0004] It has been shown that cancers that acquire resistance to cytidine analog drugs often overexpress cytidine deaminase (CDA) (Leuk. Res. 1990, 14, 751-754). Leukemic cells expressing a high level of CDA can become resistant to cytosine antimetabolites and thereby limit the antineoplastic activity of such therapeutics (Biochem. Pharmacol. 1993, 45, 1857-1861). Inhibitors of CDA, such as cedazuridine, are useful in combination chemotherapy regimens involving cytidine analog drugs.

[0005] It has been found that when azacitidine, a cytidine analog drug, is orally administered (8 mg/kg) to repeatedly phlebotomized baboon (PCV less than 20%) there is no elevation in the fetal hemoglobin levels (Hb F), indicating very minimal oral bioavailability (DeSimone et al (1985) Amer. J. of Hem. 18:283-288). The poor bioavailability of cytidine analogs is presumably due to the degradation of the cytidine analog by cytidine deaminases as well as their inherent chemical instability in the acidic gastric environment. To date, only one orally administered azacitidine product has been approved, and provides a mean oral bioavailability of approximately 11% relative to subcutaneous administration. There is a need for formulations of azacitidine which can increase bioavailability of azacitidine.

[0006] Fixed dose combination (FDC) formulations are also desirable because they can reduce the pill burden on a patient undergoing combination chemotherapy and improve patient compliance with a treatment regimen. There is need for FDC formulations comprising combinations of cytidine analogs and CDA inhibitors, and the effective dose combination of cytidine analogs and CDA inhibitors within the FDC formulations.

SUMMARY

[0007] It had been surprisingly discovered that lower dosages of cedazuridine, a CDA inhibitor were effective at increasing bioavailability of azacitidine, a cytidine analog, especially for a delayed release azacitidine formulation. The present disclosure provides a fixed dose combination (FDC) formulation that enables immediate release of cedazuridine and delayed, enteric release of azacitidine, thereby

achieving a desired level of azacitidine bioavailability and systemic exposures with a reduced amount of azacitidine, and with a lower amount of cedazuridine.

[0008] The present disclosure, in one embodiment, provides a pharmaceutical dosage form comprising: about 20 mg of cedazuridine; and about 100 mg to about 160 mg of azacitidine.

[0009] In some embodiments, the cedazuridine is formulated for immediate release. In some embodiments, at least a portion of azacitidine is formulated for enteric release. In some embodiments, azacitidine is provided as minitables comprising an enteric coat. The enteric coat may comprise polymethacrylate or copolymers thereof. The enteric coat may be sensitive to pH variations in the intestine. In some embodiments, each azacitidine minitablet comprises: about 20%-60% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitables; and one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be selected from the group consisting of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose sodium, silicon dioxide, and magnesium stearate. In some embodiments, the pharmaceutical dosage form comprises about 120 to 160 mg, about 100 to 120 mg, or about 130 to 150 mg of azacitidine. In some embodiments, the pharmaceutical dosage form comprises about 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, or 160 mg of azacitidine. In some embodiments, the cedazuridine is uncoated and in the form of minitables, a tablet, powder, blend, granules, or pellets.

[0010] Also provided herein is a capsule comprising: one or more azacitidine minitables formulated for modified release, comprising about 100 mg to about 160 mg of azacitidine, pharmaceutically acceptable excipients, and an enteric coat; and immediate release cedazuridine in a form of uncoated powder or blends, comprising about 20 mg of cedazuridine and pharmaceutically acceptable excipients. In some embodiments, the capsule comprises about 120 to 160 mg, about 100 to 120 mg, or about 130 to 150 mg of azacitidine. In some embodiments, the capsule comprises about 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, or 160 mg of azacitidine.

[0011] Also provided herein is a method of treating cancer in a patient comprising administering the dosage form or the capsule described in previous paragraphs, to the patient in need thereof.

[0012] In some embodiments, the cancer is leukemia. In some embodiments, the cancer is selected from the group consisting of previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer. In some embodiments, the method further comprises administering another therapeutic agent. The another therapeutic agent may be one or more selected from the list consisting of: ADI-PEG 20, AMG-176, APG-115, APR-246,

avelumab, bendamustine, bisantrene, brentuximab vedotin, capecitabine, CB-839, cisplatin, CS-01, cusatuzumab, cyclophosphamide, cytarabine, dasatinib, daunorubicin, DCLL9718S, decitabine, deferasirox, dexamethasone, durvalumab, eltrombopag, enasidenib, entinostat, entrectinib, enzalutamide, epacadostat, erythropoietin, etoposide, evorpacept, filgrastim, fludarabine phosphate, flumatinib, gemcitabine, gemtuzumab ozogamicin, gilteritinib, GM-CSF, GSK2879552, HMPL-523, homoharringtonine, IBI188, ibrutinib, idarubicin, itacitinib, ivosidenib, jaktinib, KPT-8602, LDE255, lenalidomide, lirilumab, LP-108, magrolimab, MAX-40279, mitoxantrone, mitoxantrone liposome, mocetinostat, moxifloxacin, nivolumab, olutasidenib, omacetaxine, oxaliplatin, paclitaxel, pembrolizumab, pevonedistat, pinometostat, pracinostat, quizartinib, revlimid, rigosertib, rituximab, romidepsin, RP7214, S64315, S65487, sabatolimab, seclidemstat, selumetinib, siremadlin, sirolimus, SL-401, SNDX-5613, sorafenib, talazoparib, tamibarotene, tolinapant, trastuzumab, tucidinostat, tyrosine kinase inhibitor, uproleselan, velcade, venetoclax, vincristine, visilizumab, vorinostat, and vosaroxin.

[0013] Also provided herein is a pharmaceutical dosage form, or a capsule described in previous paragraphs, for use in the treatment of the cancer. Also provided herein is a pharmaceutical dosage form, or a capsule described in previous paragraphs, for use in manufacturing a medicament for the treatment of the cancer.

[0014] Also provided herein is use of the pharmaceutical dosage form or a capsule described in previous paragraphs, for the treatment of the cancer. Also provided herein is use of the pharmaceutical dosage form or a capsule described in previous paragraphs, for the manufacture of medicament for the treatment of the cancer.

[0015] Also provided herein is a method of treating cancer in a patient comprising administering about 20 mg of cedazuridine; and about 100 mg to about 160 mg of azacitidine.

[0016] In some embodiments, cedazuridine and azacitidine are administered together. Cedazuridine and azacitidine may be formulated into a fixed dose combination. In some embodiments, cedazuridine and azacitidine are administered separately. In some embodiments, cedazuridine is formulated for immediate release. In some embodiments, at least a portion of azacitidine is formulated for enteric release. In some embodiments, azacitidine is provided as minitablets comprising an enteric coat. In some embodiments, the enteric coat comprises polymethacrylate or copolymers thereof. In some embodiments, the enteric coat is sensitive to pH variations in the intestine. In some embodiments, wherein the cancer is leukemia. In some embodiments, the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer. In some embodiments, the cancer is selected from previously treated or untreated, de novo or

secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) chronic myeloid leukemia (CML).

[0017] The present disclosure, in one embodiment, provides a fixed dose combination comprising: about 20 mg of cedazuridine; and about 100 mg to about 160 mg of azacitidine.

[0018] In some embodiments, the cedazuridine is formulated for immediate release. In some embodiments, at least a portion of azacitidine is formulated for enteric release. In some embodiments, azacitidine is provided as minitables comprising an enteric coat. The enteric coat may comprise polymethacrylate or copolymers thereof. The enteric coat may be sensitive to pH variations in the intestine. In some embodiments, each azacitidine minitablet comprises: about 20%-60% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitables; and one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be selected from the group consisting of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose sodium, silicon dioxide, and magnesium stearate. In some embodiments, the fixed dose combination comprises about 120 to 160 mg, about 100 to 120 mg, or about 130 to 150 mg of azacitidine. In some embodiments, the fixed dose combination comprises about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine. In some embodiments, the cedazuridine is uncoated and in the form of minitables, a tablet, powder, blend, granules, or pellets.

[0019] Also provided herein is a capsule comprising: one or more azacitidine minitables formulated for modified release, comprising about 100 mg to about 160 mg of azacitidine, pharmaceutically acceptable excipients, and an enteric coat; and immediate release cedazuridine in a form of uncoated powder or blends, comprising about 20 mg of cedazuridine and pharmaceutically acceptable excipients. In some embodiments, the capsule comprises about 120 to 160 mg, about 100 to 120 mg, or about 130 to 150 mg of azacitidine. In some embodiments, the capsule comprises about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine.

[0020] Also provided herein is a method of treating cancer in a patient comprising administering the fixed dose combination or the capsule described in previous paragraphs, to the patient in need thereof.

[0021] In some embodiments, the cancer is leukemia. In some embodiments, the cancer is selected from the group consisting of previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer. In some embodiments, the method further comprises administering another therapeutic agent. The another therapeutic agent may be

one or more selected from the list consisting of: ADI-PEG 20, AMG-176, APG-115, APR-246, avelumab, bendamustine, bisantrene, brentuximab vedotin, capecitabine, CB-839, cisplatin, CS-01, cusatuzumab, cyclophosphamide, cytarabine, dasatinib, daunorubicin, DCLL9718S, decitabine, deferasirox, dexamethasone, durvalumab, eltrombopag, enasidenib, entinostat, entrectinib, enzalutamide, epacadostat, erythropoietin, etoposide, evorpacept, filgrastim, fludarabine phosphate, flumatinib, gemcitabine, gemtuzumab ozogamicin, gilteritinib, GM-CSF, GSK2879552, HMPL-523, homoharringtonine, IBI188, ibrutinib, idarubicin, itacitinib, ivosidenib, jaktinib, KPT-8602, LDE255, lenalidomide, lirilumab, LP-108, magrolimab, MAX-40279, mitoxantrone, mitoxantrone liposome, mocetinostat, moxifloxacin, nivolumab, olutasidenib, omacetaxine, oxaliplatin, paclitaxel, pembrolizumab, pevonedistat, pinometostat, pracinostat, quizartinib, revlimid, rigosertib, rituximab, romidepsin, RP7214, S64315, S65487, sabatolimab, seclidemstat, selumetinib, siremadlin, sirolimus, SL-401, SNDX-5613, sorafenib, talazoparib, tamibarotene, tolinapant, trastuzumab, tucidinostat, tyrosine kinase inhibitor, uproleselan, velcade, venetoclax, vincristine, visilizumab, vorinostat, and vosaroxin.

[0022] Also provided herein is a fixed dose combination, or a capsule described in previous paragraphs, for use in the treatment of the cancer. Also provided herein is a fixed dose combination, or a capsule described in previous paragraphs, for use in manufacturing a medicament for the treatment of the cancer.

[0023] Also provided herein is use of the fixed dose combination or a capsule described in previous paragraphs, for the treatment of the cancer. Also provided herein is use of the fixed dose combination or a capsule described in previous paragraphs, for the manufacture of medicament for the treatment of the cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] FIG. 1 shows the dissolution release profile for azacitidine from a capsule comprising uncoated cedazuridine minitables and 75:25 and 80:20 ethyl cellulose-coated azacitidine minitables comprising intragranular and extragranular layers, according to one embodiment, at pH 6.8. (w.g. refers to weight gain from the coating).

[0025] FIG. 2 shows dissolution data for coated azacitidine minitables according to one embodiment, in going from pH 1 to pH 6.8.

[0026] FIG. 3 shows dissolution profile for coated azacitidine minitables according to one embodiment, in going from pH 1 to pH 6.8.

[0027] FIG. 4 shows dissolution profile for coated azacitidine minitables according to one embodiment, at pH 2.3, 3.0, 4.5, 5.2, 5.5, and 6.0.

[0028] FIG. 5 shows plasma exposure for azacitidine from a PK study in human subjects.

[0029] FIG. 6 shows plasma exposure for azacitidine from a PK study in human subjects.

[0030] FIG. 7 shows plasma exposure for azacitidine from a PK study in human subjects.

[0031] It will be recognized that some or all of the figures are schematic representations for purpose of illustration.

DETAILED DESCRIPTION

[0032] The stomach is a region of high acidity (about pH 1 to 3). Specific glands and organs emptying into the small intestine raise the pH of the material leaving the stomach to approximately pH 6.0 to 6.5. The large intestine and the colon are typically at about pH 6.4 to 7.0. The transit time through the small intestine is approximately three hours. In contrast, the transit time through the large intestine is approximately 35 hours. Stomach acid is believed to degrade azacitidine. Further, a longer transit time in the large intestine may lead to higher enzymatic degradation of azacitidine and consequent poor bioavailability. Accordingly, release and absorption of azacitidine outside the stomach is desirable to achieve higher bioavailability. In some embodiments, co-administration of cedazuridine, a cytidine deaminase inhibitor, may reduce enzymatic degradation of azacitidine.

[0033] In some embodiments, the fixed dose combinations or compositions described herein include a predetermined dose of azacitidine and cedazuridine, such that a desired bioavailability of azacitidine is achieved. release of azacitidine at a pH of about 6.8 in the proximal regions of the small intestine may increase absorption of azacitidine.

[0034] Azacitidine bioavailability is further enhanced by the modified-release dosage forms of azacitidine described herein. Further, variability in drug exposure is reduced. In some embodiments, the azacitidine is released at pH > 3. In some embodiments, the azacitidine is released outside the stomach. In some embodiments, enhanced absorption and/or bioavailability of azacitidine may occur when cedazuridine is co-administered and released prior to release of azacitidine. For example, cedazuridine may be released in the stomach and azacitidine may be released outside the stomach, thereby improving absorption and/or bioavailability of azacitidine.

Definitions

[0035] The following description sets forth exemplary embodiments of the present technology. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

[0036] As used in the present specification, the following words, phrases, and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0037] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*. In certain embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 1\%$. The term “about X” includes description of “X”.

[0038] The singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to “the dosage form” includes a plurality of such dosage forms.

[0039] The terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not.

[0040] The term “polymer” refers to a chemical compound or mixture of compounds consisting of repeating structural units created through a process of polymerization. Suitable polymers useful in the present dosage forms are described throughout.

[0041] A “blend” refers to a solid form wherein an active agent is mixed with additional excipients including and not limited to a bulk filler, a glidant, and/or a lubricant. The ratio of the active agent to the excipients may vary and depends on the properties of the active agent. Typically, a blend is in the form of a powder.

[0042] In some embodiments, a “granule” is a particle which has an irregular shape. In some embodiments, “granules” are solid agglomerates of powder particles.

[0043] A “pellet” is a solid mass comprising an active agent and/or additional fillers. Pellets include and are not limited to discs, beads, prolate spheroids, oblate spheroids, spheroids, cylinders, and the like. A “minitablet” is a rounded compressed solid dosage forms with a diameter smaller than tablets (i.e., equals to or less than 6 mm diameter), compressed solid mass comprising an active agent and/or additional fillers. In some embodiments, “pellet” includes “minitablet,” or vice versa. In some embodiments, “pellet” and “minitablet” may be used interchangeably. A “pellet” and/or a “minitablet” may refer to a subunit of a unit pharmaceutical dosage form, such as a capsule or a tablet.

[0044] In some embodiments, a “tablet” is a cylinder of a compressed solid mass, and typically the height of the cylinder is less than or equal to the diameter of the cylinder. In some embodiments, a “tablet” may refer to a pharmaceutical dosage form, which may include one or more subunits such as pellets, minitablets, granules, or powders.

[0045] A “FDC” or “fixed dose combination” refers to a pharmaceutical dosage form containing two or more drugs contained in a single dosage form, such as a capsule or tablet.

[0046] In some embodiments, a FDC or fixed dose combination may include two or more unit dosage forms, i.e., two or more capsules or tablets, where a single dose can be divided into. For example, a FDC or fixed dose combination may include two capsules each containing half of a single dose, and two capsules may be administered together. A single dose may be divided equally among units (e.g., capsules, tablets) or each unit may include different amount of a portion of the single dose. For example, one capsule may include greater amount of an active ingredient than another capsule within the FDC or fixed dose combination. In some embodiments, a FDC or fixed dose combination may include two or more units of a dosage form each including different drugs. For example, the FDC or fixed dose combination may include a first capsule or tablet including a first drug, and a second capsule or tablet including a second drug. Said FDC or fixed dose combination including multiple capsules or tablets, may be packaged or otherwise indicated such that a patient may be instructed to be administered a predetermined dose. For example, two capsules, each including a half of a single dose of drugs, may be packaged in one blister pack so that a patient can be administered with two capsules.

[0047] “Modified release” refers to release of a drug that occurs substantially outside of the stomach. In some embodiments, modified release is not sensitive to pH variations that occur outside of the stomach. By way of example only, hydroxypropyl methylcellulose coatings are substantially insensitive

to pH variations outside of the stomach and modified release may occur at any pH higher than the pH in the stomach. In some embodiments, modified release is pH-sensitive and release at a desired pH is achieved by use of suitable coatings. By way of example only, polymethacrylate polymer coatings such as Eudragit® are tunable and release can be modified to occur at pH > 5.5 (duodenum targeting); at pH 6–7 (jejunum); or at a pH > 7 (ileum and colon).

[0048] “Enteric release” refers to release of a drug substantially in the intestine to prevent the degradation of the drug from acid-catalyzed hydrolysis in the stomach. “Enteric coat” or “enteric coating” refers to a coating that allows for release of a drug substantially in the intestine. In some embodiments, enteric release is “delayed release” or “timed release” which is pH-sensitive and occurs at pH > 5.5 (duodenum targeting); at pH 6–7 (jejunum); or at a pH > 7 (ileum and colon). “Delayed release coating” or “delayed release coat” refers to a coating that is sensitive to pH variations in the intestine and release of a drug is delayed till the target pH environment is available. In some embodiments, an enteric coating is a delayed release coating.

[0049] “Seal coat” refers to a coating which is layered onto an uncoated pellet prior to coating it with an enteric coating. The seal coat forms an intermediate layer and prevents interaction between the core comprising the active agent and the enteric coat. In some embodiments, the seal coat comprises a polymer that allows for intermediate release.

[0050] The term “% w/w” of a component as used herein refers to the weight of the component based on the total weight of a dosage form comprising the component. For example, if component A is present in an amount of 50% w/w in a 100 mg dosage form, component A is present in an amount of 50 mg.

[0051] The term “bulk fillers” refers to chemical compounds that are used to dilute the compound of interest. Bulk fillers can also serve to stabilize compounds. Non-limiting examples of bulk fillers include starch, saccharides, disaccharides, sucrose, lactose, polysaccharides, cellulose, cellulose ethers, hydroxypropyl cellulose, sugar alcohols, xylitol, sorbitol, maltitol, microcrystalline cellulose, calcium or sodium carbonate, lactose, lactose monohydrate, dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, mannitol, microcrystalline cellulose, and tribasic calcium phosphate.

[0052] The term “glidant” refers to an excipient used to promote powder flow by reducing interparticle friction and cohesion. Glidants may improve flow-properties during tablet compression and produce an anti-caking effect. Non-limiting examples of glidants include colloidal silicon dioxide, talc, fumed silica, starch, starch derivatives, magnesium carbonate, and bentonite. Glidants are typically used in conjunction with lubricants.

[0053] The term “lubricant” refers to an excipient which is added to a powder blend to prevent the compacted powder mass from sticking to the equipment during processing. It aids the ejection of a compacted solid mass from dies, and can improve powder flow. Non-limiting examples of lubricants include magnesium stearate, stearic acid, silica, fats, calcium stearate, polyethylene glycol, sodium stearyl fumarate, talc, and solubilizers such as fatty acids including lauric acid, oleic acid, and C8/C10 fatty acids.

[0054] “Substantially” all of the azacitidine means greater than 70%; or greater than 75%; or greater than 80%; or greater than 85%; or greater than 90%; or greater than 95%; or greater than 99% of the azacitidine. Release of a drug “substantially” outside the stomach means greater than 70%; or greater than 75%; or greater than 80%; or greater than 85%; or greater than 90%; or greater than 95%; or greater than 99% of the drug is released outside of the stomach.

[0055] “pH variations in the intestine” refers to the changes in pH within the intestinal lumen in going from the stomach to the rectum. For instance, pH in the duodenum is about 5.5 or higher; pH in the jejunum is about 6–7; pH in the ileum and colon is about 7 or higher; pH in the cecum is about 5.7; pH in the rectum is about 6.7.

[0056] An enteric coating which is “not sensitive to pH” refers to a coating that may allow for release of a drug at any pH that occurs outside the stomach. An enteric coating which is “sensitive to pH” may allow for release of a drug at a targeted pH, for example a targeted area within the intestinal lumen.

[0057] As used herein, “hydroxypropyl methylcellulose” is used interchangeably with “HPMC” and/or “Hypromellose”. “HPMC” includes Hypromellose acetate succinate (HPMCAS) and/or grades of HPMCAS which are commercially available.

[0058] As used herein Eudragit® refers to a class of polymethacrylate-based copolymers. It includes anionic, cationic, and/or neutral copolymers based on methacrylic acid and methacrylic/acrylic esters or their derivatives. Various grades of the polymers are commercially available including and not limited to L 30 D-55, FS 30 D, and FL 30 D-55. Anionic Eudragit® L dissolves at pH > 6 and is used for enteric coating, while Eudragit® S, soluble at pH > 7 is used for colon targeting. Combinations of Eudragit® S and Eudragit® L can provide drug release at pH < 7. Eudragit® RL and RS, having quaternary ammonium groups, are water insoluble, but swellable/permeable polymers which are suitable for the sustained release film coating applications.

[0059] “Cedazuridine” includes epimers of cedazuridine and is not limited to the isomer drawn herein.

[0060] “Amino acid salts” in the context of buffers refers to buffer salts comprising one or more amino acids, e.g., histidine, glycine, or any other amino acid known to one of skill in the art. Amino acids contain positively charged amino groups and negatively charged carboxyl groups. The charged regions of these molecules can bind hydrogen and hydroxyl ions, and thus function as buffers.

[0061] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0062] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, a divalent heteroaryl group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group (for example, methylenyl, ethylenyl, and propylenyl), an “arylene” group or an “arylenyl” group (for example, phenylenyl or naphthylenyl, or quinolinyl for heteroarylene), respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, e.g., arylalkyl or aralkyl, the last-mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[0063] “Alkyl” refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (*i.e.*, C₁₋₂₀ alkyl), 1 to 8 carbon atoms (*i.e.*, C₁₋₈ alkyl), 1 to 6 carbon atoms (*i.e.*, C₁₋₆ alkyl), or 1 to 4 carbon atoms (*i.e.*, C₁₋₄ alkyl). Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, “butyl” includes n-butyl (*i.e.* -(CH₂)₃CH₃), sec-butyl (*i.e.* -CH(CH₃)CH₂CH₃), isobutyl (*i.e.* -CH₂CH(CH₃)₂) and tert-butyl (*i.e.* -C(CH₃)₃); and “propyl” includes n-propyl (*i.e.* -(CH₂)₂CH₃) and isopropyl (*i.e.* -CH(CH₃)₂).

[0064] “Alkenyl” refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (*i.e.*, C₂₋₂₀ alkenyl), 2 to 8 carbon atoms (*i.e.*, C₂₋₈ alkenyl), 2 to 6 carbon atoms (*i.e.*, C₂₋₆ alkenyl), or 2 to 4 carbon atoms (*i.e.*, C₂₋₄ alkenyl). Examples of alkenyl groups include ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[0065] “Alkynyl” refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (*i.e.*, C₂₋₂₀ alkynyl), 2 to 8 carbon atoms (*i.e.*, C₂₋₈ alkynyl), 2 to 6 carbon atoms (*i.e.*, C₂₋₆ alkynyl), or 2 to 4 carbon atoms (*i.e.*, C₂₋₄ alkynyl). The term “alkynyl” also includes those groups having one triple bond and one double bond.

[0066] “Alkoxy” refers to the group “alkyl-O-”. Examples of alkoxy groups include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy.

[0067] “Alkoxyalkyl” refers to the group “alkyl-O-alkyl”.

[0068] “Alkylthio” refers to the group “alkyl-S-”. “Alkylsulfinyl” refers to the group “alkyl-S(O)-”. “Alkylsulfonyl” refers to the group “alkyl-S(O)₂-”. “Alkylsulfonylalkyl” refers to -alkyl-S(O)₂-alkyl.

[0069] “Acyl” refers to a group -C(O)R^y, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, e.g., formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl, and benzoyl.

[0070] “Amido” refers to both a “C-amido” group which refers to the group -C(O)NR^yR^z and an “N-amido” group which refers to the group -NR^yC(O)R^z, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a cycloalkyl or heterocyclyl; each of which may be optionally substituted, as defined herein.

[0071] “Amino” refers to the group -NR^yR^z wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0072] “Amidino” refers to -C(NR^y)(NR^z)₂, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0073] “Aryl” refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (*i.e.*, C₆₋₂₀ aryl), 6 to 12 carbon ring atoms (*i.e.*, C₆₋₁₂ aryl), or 6 to 10 carbon ring atoms (*i.e.*, C₆₋₁₀ aryl). Examples of aryl groups include phenyl, naphthyl, fluorenyl, and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

[0074] “Arylalkyl” or “Aralkyl” refers to the group “aryl-alkyl”.

[0075] “Carbamoyl” refers to both an “O-carbamoyl” group which refers to the group -O-C(O)NR^yR^z and an “N-carbamoyl” group which refers to the group -NR^yC(O)OR^z, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0076] “Carboxyl ester” or “ester” refer to both -OC(O)R^x and -C(O)OR^x, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0077] “Cyanoalkyl” refers to an alkyl group as defined above, wherein one or more (e.g., 1 or 2) hydrogen atoms are replaced by a cyano (-CN) group.

[0078] “Cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (*i.e.*, the cyclic group having at least one double bond). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (*i.e.*, C₃₋₂₀ cycloalkyl), 3 to 12 ring carbon atoms (*i.e.*, C₃₋₁₂ cycloalkyl), 3 to 10 ring carbon atoms (*i.e.*, C₃₋₁₀ cycloalkyl), 3 to 8 ring carbon atoms (*i.e.*, C₃₋₈ cycloalkyl), or 3 to 6 ring carbon atoms (*i.e.*, C₃₋₆ cycloalkyl). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0079] “Cycloalkylalkyl” refers to the group “cycloalkyl-alkyl”.

[0080] “Imino” refers to a group -C(NR^y)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0081] “Imido” refers to a group -C(O)NR^yC(O)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0082] “Halogen” or “halo” refers to atoms occupying group VIIA of the periodic table, such as fluoro, chloro, bromo, or iodo.

[0083] “Haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of

haloalkyl include, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0084] “Haloalkoxy” refers to an alkoxy group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0085] “Haloalkoxyalkyl” refers to an alkoxyalkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a halogen.

[0086] “Hydroxyalkyl” refers to an alkyl group as defined above, wherein one or more (e.g., 1 to 6 or 1 to 3) hydrogen atoms are replaced by a hydroxy group.

[0087] “Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms), excluding any terminal carbon atom(s), are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR^y-, -O-, -S-, -S(O)-, -S(O)₂-, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, e.g., ethers (e.g., -CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, etc.), thioethers (e.g., -CH₂SCH₃, -CH(CH₃)SCH₃, -CH₂CH₂SCH₃, -CH₂CH₂SCH₂CH₂SCH₃, etc.), sulfones (e.g., -CH₂S(O)₂CH₃, -CH(CH₃)S(O)₂CH₃, -CH₂CH₂S(O)₂CH₃, -CH₂CH₂S(O)₂CH₂CH₂OCH₃, etc.), and amines (e.g., -CH₂NR^yCH₃, -CH(CH₃)NR^yCH₃, -CH₂CH₂NR^yCH₃, -CH₂CH₂NR^yCH₂CH₂NR^yCH₃, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). As used herein, heteroalkyl includes 2 to 10 carbon atoms, 2 to 8 carbon atoms, or 2 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[0088] “Heteroaryl” refers to an aromatic group having a single ring, multiple rings, or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C₁₋₂₀ heteroaryl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heteroaryl), or 3 to 8 carbon ring atoms (i.e., C₃₋₈ heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. In certain instances, heteroaryl includes 5-10 membered ring systems, 5-7 membered ring systems, or 5-6 membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen, and sulfur. Examples of heteroaryl groups include, e.g., acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl,

phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinoliny, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, thiophenyl (i.e., thienyl), tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinoliny, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound *via* either ring of the fused system. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0089] “Heteroarylalkyl” refers to the group “heteroaryl-alkyl”.

[0090] “Heterocyclyl” refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups, and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged, or spiro, and may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide (-O⁻) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to a cycloalkyl, an aryl, or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C₂₋₂₀ heterocyclyl), 2 to 12 ring carbon atoms (i.e., C₂₋₁₂ heterocyclyl), 2 to 10 ring carbon atoms (i.e., C₂₋₁₀ heterocyclyl), 2 to 8 ring carbon atoms (i.e., C₂₋₈ heterocyclyl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ heterocyclyl), 3 to 8 ring carbon atoms (i.e., C₃₋₈ heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C₃₋₆ heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur, or oxygen. Examples of heterocyclyl groups include, e.g., azetidiny, azepiny, benzodioxolyl, benzo[b][1,4]dioxepiny, 1,4-benzodioxany, benzopyrany, benzodioxiny, benzopyranony, benzofuranony, dioxolany, dihydropyrany, hydropyrany, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanony, imidazoliny, imidazolidiny, indoliny, indoliziny, isoindoliny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, oxirany, oxetany, phenothiaziny, phenoxaziny, piperidinyl, piperazinyl, 4-piperidony, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, tetrahydropyrany, trithianyl, tetrahydroquinoliny, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, and 1,1-dioxo-thiomorpholiny. The term “heterocyclyl” also includes “spiroheterocyclyl” when there are two positions for substitution on the same carbon atom. Examples of the spiro-heterocyclyl rings include, e.g., bicyclic and tricyclic ring systems, such as oxabicyclo[2.2.2]octany, 2-oxa-7-azaspiro[3.5]nonany, 2-oxa-6-azaspiro[3.4]octany, and 6-oxa-1-azaspiro[3.3]heptany. Examples of the fused-heterocyclyl

rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinoliny, 4,5,6,7-tetrahydrothieno[2,3-c]pyridiny, indoliny, and isoindoliny, where the heterocyclyl can be bound *via* either ring of the fused system.

[0091] “Heterocyclalkyl” refers to the group “heterocycl-alkyl-.”

[0092] “Oxime” refers to the group $-CR^y(=NOH)$ wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0093] “Sulfonyl” refers to the group $-S(O)_2R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl, and toluenesulfonyl.

[0094] “Sulfinyl” refers to the group $-S(O)R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl, and toluenesulfinyl.

[0095] “Sulfonamido” refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein.

[0096] The terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term “optionally substituted” refers to any one or more hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[0097] The term “substituted” used herein means any of the above groups (i.e., alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, and/or heteroalkyl) wherein at least one (e.g., 1 to 5 or 1 to 3) hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanadino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclalkyl, $-NHNH_2$, $=NNH_2$, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, $-S(O)OH$, $-S(O)_2OH$, sulfonamido, thiol, thioxo, N-oxide, or $-Si(R^y)_3$, wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl.

[0098] In certain embodiments, “substituted” includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NR^gR^h$, $-NR^gC(O)R^h$, $-NR^gC(O)NR^gR^h$, $-NR^gC(O)OR^h$, $-NR^gS(O)_{1-2}R^h$, $-C(O)R^g$, $-C(O)OR^g$, $-OC(O)OR^g$, $-OC(O)R^g$, $-C(O)NR^gR^h$,

-OC(O)NR^gR^h, -OR^g, -SR^g, -S(O)R^g, -S(O)₂R^g, -OS(O)₁₋₂R^g, -S(O)₁₋₂OR^g, -NR^gS(O)₁₋₂NR^gR^h, =NSO₂R^g, =NOR^g, -S(O)₁₋₂NR^gR^h, -SF₅, -SCF₃, or -OCF₃. In certain embodiments, “substituted” also means any of the above groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are replaced with -C(O)R^g, -C(O)OR^g, -C(O)NR^gR^h, -CH₂SO₂R^g, or -CH₂SO₂NR^gR^h. In the foregoing, R^g and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, and/or heteroarylalkyl. In certain embodiments, “substituted” also means any of the above groups in which one or more (e.g., 1 to 5 or 1 to 3) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxy, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^g and R^h and Rⁱ are taken together with the atoms to which they are attached to form a heterocycl ring optionally substituted with oxo, halo, or alkyl optionally substituted with oxo, halo, amino, hydroxy, or alkoxy.

[0099] Some of the compounds exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown, and regardless of the nature of the equilibrium among tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[0100] In many cases, the compounds of this disclosure, i.e., azacitidine and cedazuridine, are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[0101] Provided are also pharmaceutically acceptable salts, hydrates, tautomeric forms, polymorphs, and prodrugs of the compounds described herein. “Pharmaceutically acceptable” or “physiologically acceptable” refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[0102] The term “pharmaceutically acceptable salt” of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. “Pharmaceutically acceptable salts” or “physiologically acceptable salts” include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include, e.g., acetic acid, propionic acid,

gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of NH_3 , or primary, secondary, tertiary amines, such as salts derived from a N-containing heterocycle, a N-containing heteroaryl, or derived from an amine of formula $\text{N}(\text{R}^{\text{N}})_3$ (e.g., $\text{HN}^+(\text{R}^{\text{N}})_3$ or $(\text{alkyl})\text{N}^+(\text{R}^{\text{N}})_3$) where each R^{N} is independently hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each is optionally substituted, such as by one or more (e.g., 1-5 or 1-3) substituents (e.g., halo, cyano, hydroxy, amino, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, or haloalkoxy). Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(iso-propyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0103] As used herein, “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0104] “Treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (e.g., metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (e.g., ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival.

[0105] “Prevention” or “preventing” means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0106] “Subject” refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation, or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In one embodiment, the subject is a human.

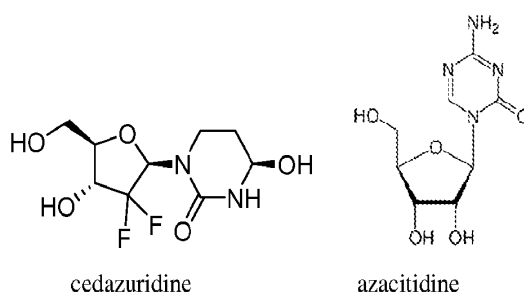
[0107] The term “therapeutically effective amount” or “effective amount” of a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of T-cell lymphoma. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0108] “Medicament” or “medicaments” as referred to herein may be prepared by conventional processes, including the combination of one or more compounds according to the present disclosure and a pharmaceutically acceptable carrier. For example, in the context of this disclosure, medicament may include both azacitidine and cedazuridine.

Combinations of Azacitidine and Cedazuridine

[0109] In one embodiment, provided herein is a pharmaceutical dosage form or composition comprising azacitidine or a pharmaceutically acceptable salt thereof. The pharmaceutical dosage form or composition may further include a CDA inhibitor, such as cedazuridine, or a pharmaceutically acceptable salt thereof, such that the bioavailability of azacitidine is enhanced.

[0110] In one embodiment, provided herein is a fixed dose combination, a pharmaceutical dosage form or a composition comprising cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a pharmaceutically acceptable salt thereof. The chemical structures of both cedazuridine and azacitidine are shown below.



Release Profile of Azacitidine

[0111] It has now been discovered that enteric release of azacitidine in the intestine is more advantageous for the bioavailability of azacitidine, as compared to gastric release, and at least a portion of azacitidine in the pharmaceutical dosage form or composition may be formulated such that it is released in intestine, not in the stomach. In one embodiment, a fixed dose combination, a pharmaceutical dosage form or a composition comprises azacitidine, or a pharmaceutically acceptable salt thereof, wherein at least a portion of the azacitidine is formulated for modified release. For example, about 5%, 10%, 15%, 20%, 25%, 30%, 33.3%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%,

90%, 95% or 100% of the azacitidine, by weight, may be formulated for modified release. In some embodiments, about 1/3, or 2/3 of the azacitidine, by weight based on the total weight of the azacitidine in the tablet or capsule, may be formulated for modified release. In some embodiments, none of the azacitidine is formulated for immediate release (e.g., release in the stomach) and the azacitidine is formulated for modified release. In some of such embodiments, the azacitidine formulated for modified release is coated. In some embodiments, the coated azacitidine is in the form of pellets. In some embodiments, the coated azacitidine is in the form of minitabket.

[0112] In some embodiments of the pharmaceutical dosage form, the portion of azacitidine that is formulated for modified release is formulated for enteric release. In some of such embodiments, the portion of the azacitidine that is formulated for modified release is formulated for enteric release that is delayed release at a targeted pH (e.g., pH of duodenum, the jejunum, the ileum, or the colon). In some embodiments of the pharmaceutical dosage form, the portion of azacitidine that is formulated for immediate release is provided as uncoated minitabkets or pellets. Such uncoated minitabkets or pellets form cores which are optionally coated with release modifying coatings. In some embodiments of the pharmaceutical dosage form, the portion of azacitidine that is formulated for modified release is provided as enteric-coated minitabkets or pellets. In some embodiments, the enteric coating, or the release modifying coating is pH sensitive.

[0113] In some embodiments at least a portion of the azacitidine is formulated for immediate release (e.g., release in the stomach). For example, about 5%, 10%, 15%, 20%, 25%, 30%, 33.3%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the azacitidine, by weight, may be formulated for immediate release. In some embodiments, about 1/3, or 2/3 of the azacitidine, by weight, may be formulated for immediate release. In some of such embodiments, the azacitidine formulated for immediate release is uncoated. In some embodiments the uncoated azacitidine is a powder. In some embodiments the uncoated azacitidine is a blend (e.g., powder blend). In some embodiments the uncoated azacitidine is in the form of granules. In some embodiments, the uncoated azacitidine is in the form of pellets. In some embodiments, the uncoated azacitidine is in the form of minitabkets.

[0114] In some embodiments of the pharmaceutical dosage form, about 0% to about 60% of the azacitidine is provided as uncoated minitabkets or pellets and about 100% to about 50% of the azacitidine is provided as modified release coated minitabkets or pellets. In some embodiments of the pharmaceutical dosage form, about 0% to about 70% of the azacitidine is provided as uncoated minitabkets or pellets and about 100% to about 30% of the azacitidine is provided as modified release coated minitabkets or pellets. In some embodiments of the pharmaceutical dosage form, about 10% to about 65% of the azacitidine is provided as uncoated minitabkets or pellets and about 90% to about 35% of the azacitidine is provided as modified release coated minitabkets or pellets. In some embodiments of the pharmaceutical dosage form, about 20% to about 60% of the azacitidine is provided as uncoated minitabkets or pellets and about 80% to about 40% of the azacitidine is provided as modified release coated minitabkets or pellets. In some embodiments of the pharmaceutical dosage form, about 30% to about 65% of the azacitidine is provided

as uncoated minitabets or pellets and about 70% to about 35% of the azacitidine is provided as modified release coated minitabets or pellets. In some embodiments of the pharmaceutical dosage form, about 30% to about 60% of the azacitidine is provided as uncoated minitabets or pellets and about 70% to about 40% of the azacitidine is provided as modified release coated minitabets or pellets. In some embodiments of the pharmaceutical dosage form, about 37% to about 60% of the azacitidine is provided as uncoated minitabets or pellets and about 40% to about 63% of the azacitidine is provided as modified release coated minitabets or pellets.

[0115] In some embodiments of the pharmaceutical dosage form, all of the azacitidine is formulated for modified release. In some embodiments of the pharmaceutical dosage form, none of the azacitidine is formulated for immediate release. In some embodiments of the pharmaceutical dosage form, substantially all of the azacitidine is formulated for modified release. In some of such embodiments, substantially all of the azacitidine is released outside of the stomach (e.g., in the intestine).

Release Profile of Cedazuridine

[0116] While cedazuridine enhances bioavailability of azacitidine, the location of release of cedazuridine affects the enhancement of bioavailability of azacitidine, and it has been discovered that immediate release (release in stomach) of cedazuridine further helps the enhancement of bioavailability of azacitidine.

[0117] In one embodiment, a fixed dose combination, a pharmaceutical dosage form or a composition comprises cedazuridine or a pharmaceutically acceptable salt thereof, and azacitidine or a pharmaceutically acceptable salt thereof, wherein at least a portion of the cedazuridine is formulated for immediate release. In some embodiments, a portion of the cedazuridine is formulated for immediate release, and the remainder of the cedazuridine is formulated for modified release. For example, about 5%, 10%, 15%, 20%, 25%, 30%, 33.3%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the cedazuridine, by weight, may be formulated for immediate release. In some embodiments, about 1/3, or 2/3 of the cedazuridine, by weight, may be formulated for immediate release. In some embodiments the cedazuridine is formulated for immediate release, and none of the cedazuridine is formulated for modified release. In some embodiments, substantially all of the cedazuridine is formulated for immediate release. In some of such embodiments, the cedazuridine formulated for immediate release is uncoated. In some embodiments the uncoated cedazuridine is a powder. In some embodiments, the uncoated cedazuridine is a blend (e.g., powder blend). In some embodiments, the uncoated cedazuridine is in the form of granules. In some embodiments, the uncoated cedazuridine is in the form of pellets. In some embodiments the uncoated cedazuridine is in the form of minitabets. In some embodiments of the pharmaceutical dosage form, the portion of cedazuridine that is formulated for modified release is formulated for enteric release. In some embodiments of the pharmaceutical dosage form, the portion of cedazuridine that is formulated for immediate release is provided as uncoated minitabets or pellets. Such uncoated minitabets or pellets form cores which are optionally coated with release modifying coatings.

Dosage

[0118] In some embodiments, the pharmaceutical dosage form comprises about 1 to about 200 mg, about 1 to about 150 mg, about 5 to about 100 mg, about 5 to about 80 mg, about 5 to about 60 mg, about 10 to about 60 mg, about 5 to about 50 mg, about 10 to about 50 mg, about 10 to about 40 mg, about 5 to about 40 mg, about 10 to about 30 mg, about 5 to about 30 mg, about 5 to about 25 mg, about 10 to about 25 mg, about 15 to about 50 mg, about 15 to about 40 mg, about 15 to about 30 mg, about 15 to about 25 mg, about 30 to 50 mg, or about 50 mg to 70 mg of cedazuridine, as an active pharmaceutical ingredient. In some embodiments, the pharmaceutical dosage form comprises about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, or 100 mg of cedazuridine, as an active pharmaceutical ingredient.

[0119] In some embodiments, the pharmaceutical dosage form comprises about 20 to about 160 mg, about 30 to about 160 mg, about 40 to about 160 mg, about 50 to about 160 mg, about 60 to about 160 mg, about 70 to about 160 mg, about 80 to about 160 mg, about 90 to about 170 mg, or about 100 to about 160 mg, preferably about 120 to about 160 mg of azacitidine, as an active pharmaceutical ingredient. In some embodiments, the pharmaceutical dosage form comprises about 100 to about 120 mg, about 110 to about 130 mg, about 120 to about 140 mg, about 130 to about 150 mg, about 140 to about 160 mg, or about 136 to about 144 mg of azacitidine, as an active pharmaceutical ingredient. In some embodiments, the pharmaceutical dosage form comprises about 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, or 160 mg of azacitidine, as an active pharmaceutical ingredient.

[0120] Any suitable amount of azacitidine or cedazuridine described herein may be administered to a patient. For example, a patient may be administered about 10 to about 60 mg of cedazuridine and about 100 to about 160 mg of azacitidine; about 10 to about 60 mg of cedazuridine and about 120 to about 160 mg of azacitidine; about 10 to about 60 mg of cedazuridine and about 100 to about 120 mg of azacitidine; about 10 to about 60 mg of cedazuridine and about 110 to about 130 mg of azacitidine; about 10 to about 60 mg of cedazuridine and about 120 to about 140 mg of azacitidine; about 10 to about 60 mg of cedazuridine and about 130 to about 150 mg of azacitidine; or about 10 to about 60 mg of cedazuridine and about 140 to about 160 mg of azacitidine. In some embodiments, a patient may be administered about 20 mg of cedazuridine and about 100 to about 160 mg of azacitidine; about 20 mg of cedazuridine and about 120 to about 160 mg of azacitidine; about 20 mg of cedazuridine and about 100 to about 120 mg of azacitidine; about 20 mg of cedazuridine and about 110 to about 130 mg of azacitidine; about 20 mg of cedazuridine and about 120 to about 140 mg of azacitidine; about 20 mg of cedazuridine and about 130 to about 150 mg of azacitidine; or about 20 mg of cedazuridine and about 140 to about 160 mg of azacitidine. In some embodiments, the patient may be administered the aforementioned dose once per day.

[0121] In some embodiments, a patient may be administered about 20 mg of cedazuridine and about 100 mg of azacitidine; about 20 mg of cedazuridine and about 104 mg of azacitidine; about 20 mg of

cedazuridine and about 108 mg of azacitidine; about 20 mg of cedazuridine and about 112 mg of azacitidine; about 20 mg of cedazuridine and about 116 mg of azacitidine; about 20 mg of cedazuridine and about 120 mg of azacitidine; about 20 mg of cedazuridine and about 124 mg of azacitidine; about 20 mg of cedazuridine and about 128 mg of azacitidine; about 20 mg of cedazuridine and about 132 mg of azacitidine; about 20 mg of cedazuridine and about 136 mg of azacitidine; about 20 mg of cedazuridine and about 140 mg of azacitidine; about 20 mg of cedazuridine and about 144 mg of azacitidine; about 20 mg of cedazuridine and about 148 mg of azacitidine; about 20 mg of cedazuridine and about 152 mg of azacitidine; about 20 mg of cedazuridine and about 156 mg of azacitidine; or about 20 mg of cedazuridine and about 160 mg of azacitidine.

[0122] Any suitable combination of content of azacitidine and cedazuridine described herein may be administered together or separately.

[0123] Any suitable combination of content of azacitidine and cedazuridine described herein, may be included in a fixed dose combination dosage form.

[0124] In some embodiments, the fixed dose combination may include two or more unit dosage forms (e.g., two or more capsules or tablets), and a single dose of cedazuridine and/or azacitidine may be contained within two or more unit dosage forms (e.g., two or more capsules or tablets). In this specification, the “fixed dose combination” may refer to a single dosage form (e.g., capsule or tablet) or a set of two or more unit dosage forms (e.g., capsules or tablets), unless specified otherwise. In some embodiments, the two or more unit dosage forms (e.g., capsules or tablets) of the fixed dose combination may be packaged together, such that a patient or a clinician can easily administer them together.

[0125] For example, the fixed dose combination may include about 10 to about 60 mg of cedazuridine and about 100 to about 160 mg of azacitidine. In some of such embodiments, the fixed dose combination may include about 10 to about 60 mg of cedazuridine and about 120 to about 160 mg of azacitidine. In some of such embodiments, the fixed dose combination may include about 10 to about 60 mg of cedazuridine and about 100 to about 120 mg of azacitidine. In some of such embodiments, the fixed dose combination may include about 10 to about 60 mg of cedazuridine and about 110 to about 130 mg of azacitidine, about 10 to about 60 mg of cedazuridine and about 120 to about 140 mg of azacitidine, about 10 to about 60 mg of cedazuridine and about 130 to about 150 mg of azacitidine, or about 10 to about 60 mg of cedazuridine and about 140 to about 160 mg of azacitidine of azacitidine. In some embodiments, the fixed dose combination may include about 20 mg of cedazuridine and about 100 to about 160 mg of azacitidine. In some of such embodiments, the fixed dose combination may include about 20 mg of cedazuridine and about 120 to about 160 mg of azacitidine. In some of such embodiments, the fixed dose combination may include about 20 mg of cedazuridine and about 100 to about 120 mg of azacitidine. In some of such embodiments, the fixed dose combination may include about 20 mg of cedazuridine and about 110 to about 130 mg of azacitidine, about 20 mg of cedazuridine and about 120 to about 140 mg of azacitidine, about 20 mg of cedazuridine and about 130 to about 150 mg of azacitidine, or about 20 mg of cedazuridine and about 140 to about 160 mg of azacitidine of azacitidine.

include about 60 mg of cedazuridine and about 152 mg of azacitidine. In some embodiments, the fixed dose combination may include about 60 mg of cedazuridine and about 156 mg of azacitidine. In some embodiments, the fixed dose combination may include about 60 mg of cedazuridine and about 160 mg of azacitidine.

[0130] In some embodiments, the fixed dose combination may include two capsules or tablets, each including cedazuridine and azacitidine. For example, each of the two capsules or tablets may include about: 5 to about 30 mg of cedazuridine and about 50 to about 80 mg of azacitidine; about 5 to about 30 mg of cedazuridine and about 60 to about 80 mg of azacitidine; about 5 to about 30 mg of cedazuridine and about 55 to about 65 mg of azacitidine; about 5 to about 30 mg of cedazuridine and about 60 to about 70 mg of azacitidine; about 5 to about 30 mg of cedazuridine and about 65 to about 75 mg of azacitidine; or about 5 to about 30 mg of cedazuridine and about 70 to about 80 mg of azacitidine of azacitidine.

[0131] In some embodiments, the fixed dose combination may include two unit dosage forms (e.g., capsules or tablets), each including about 10 mg of cedazuridine and about 50 to about 80 mg of azacitidine; about 10 mg of cedazuridine and about 60 to about 80 mg of azacitidine; about 10 mg of cedazuridine and about 50 to about 60 mg of azacitidine; about 10 mg of cedazuridine and about 55 to about 65 mg of azacitidine; about 10 mg of cedazuridine and about 60 to about 70 mg of azacitidine; about 10 mg of cedazuridine and about 65 to about 75 mg of azacitidine; or about 10 mg of cedazuridine and about 70 to about 80 mg of azacitidine of azacitidine.

[0132] In some embodiments, the fixed dose combination may include two unit dosage forms (e.g., capsules or tablets), each including about 10 mg of cedazuridine and about 50 mg of azacitidine; about 10 mg of cedazuridine and about 52 mg of azacitidine; about 20 mg of cedazuridine and about 54 mg of azacitidine; about 10 mg of cedazuridine and about 56 mg of azacitidine. about 10 mg of cedazuridine and about 58 mg of azacitidine; about 10 mg of cedazuridine and about 60 mg of azacitidine; about 10 mg of cedazuridine and about 62 mg of azacitidine; about 10 mg of cedazuridine and about 64 mg of azacitidine; about 10 mg of cedazuridine and about 66 mg of azacitidine; about 10 mg of cedazuridine and about 68 mg of azacitidine; about 10 mg of cedazuridine and about 70 mg of azacitidine; about 10 mg of cedazuridine and about 72 mg of azacitidine; about 10 mg of cedazuridine and about 74 mg of azacitidine; about 10 mg of cedazuridine and about 76 mg of azacitidine. In some embodiments, the fixed dose combination may include about 10 mg of cedazuridine and about 78 mg of azacitidine. In some embodiments, the fixed dose combination may include about 10 mg of cedazuridine and about 80 mg of azacitidine.

[0133] In some embodiments, the fixed dose combination may include two or more unit dosage forms (e.g., capsules or tablets) including different amount of cedazuridine and/or azacitidine, each selected from aforementioned unit dosage forms. For example, the fixed dose combination may include two unit dosage forms (e.g., capsules or tablets), one including about 10 mg of cedazuridine and about 68 mg of azacitidine and the other one including about 10 mg of cedazuridine and about 72 mg of azacitidine.

[0134] In some embodiments, cedazuridine and azacitidine may be separated. For example, the fixed dose combination may include two or more unit dosage forms (e.g., capsules or tablets), one including cedazuridine only and the other(s) including azacitidine only. In some embodiments, one capsule or tablet may include about 10, 20, or 40 mg of cedazuridine, while the other capsule or tablet(s) may include about 132, 136, 140, 144, or 148 mg of azacitidine.

[0135] In some embodiments, the pharmaceutical dosage form or the fixed dose combination may include cedazuridine and azacitidine in the ratio of from about 1:8 to about 1:5, or from about 1:8 to about 1:6 by weight of cedazuridine and azacitidine. In some embodiments, the pharmaceutical dosage form or the fixed dose combination may include cedazuridine and azacitidine in the ratio of from about 1:10 to about 1:1, from about 1:8 to about 1:1, from about 1:8 to about 1:2, from about 1:8 to about 1:3, from about 1:8 to about 1:4, from about 1:8 to about 1:7.5, from about 1:7.5 to about 1:7, from about 1:7 to about 1:6.5, from about 1:6.5 to about 1:6, from about 1:6 to about 1:5.5, or from about 1:5.5 to about 1:5, by weight of cedazuridine and azacitidine. In some embodiments, the fixed dose combination may include cedazuridine and azacitidine in the ratio of about 1:1, about 1:1.5, about 1:2, about 1:2.5, about 3:4, about 3:5, about 1:3, about 1:4, about 1:5, about 1:6, about 1:6.5, about 1:7, about 1:7.5, about 1:8, about 1.5:1, about 2:1, about 2.5:1, about 4:3, about 4:1, or about 5:3 by weight of cedazuridine and azacitidine.

[0136] The specific dose level of a composition of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of cedazuridine and/or azacitidine between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject. Also, population pharmacokinetic modeling and simulation may be used to predict optimal dosage for different race/ethnicity.

[0137] The daily dosage may also be described as a total amount of cedazuridine and/or azacitidine administered per dose or per day. Daily dosage of cedazuridine and/or azacitidine may be between about 1 mg and 4,000 mg, between about 2,000 to 4,000 mg/day, between about 1 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 10 to 500 mg/day, between about 20 to 500 mg/day, between about 50 to 300 mg/day, between about 75 to 200 mg/day, or between about 15 to 150 mg/day.

[0138] When administered orally, the total daily dosage for a human subject may be between 1 mg and 1,000 mg, between about 1,000-2,000 mg/day, between about 10-500 mg/day, between about 50-300 mg/day, between about 75-200 mg/day, or between about 100-150 mg/day.

[0139] In some embodiments, the daily dosage of cedazuridine for a human subject may be about 5 to about 200 mg, about 10 to about 300 mg, about 20 to about 300 mg, about 20 to about 200 mg, about 20 to about 100 mg, about 5 to about 100 mg, about 5 to about 80 mg, about 20 to about 80 mg, about 5 to about 60 mg, about 20 to about 60 mg, about 5 to about 50 mg, about 30 to about 50 mg, about 10 to about 30 mg, about 30 to about 300 mg, about 40 to about 300 mg, about 50 to about 300 mg, about 50 to about 250 mg, about 50 to about 200 mg, about 60 to about 150 mg, about 70 to about 150 mg, about 70 to about 140 mg, about 80 to about 130 mg, about 90 to about 120 mg, about 90 to about 110 mg, about 10 to about 100 mg, about 10 to about 70 mg, about 20 to about 50 mg per day. In some embodiments, the daily dosage of cedazuridine for a human subject may be about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 mg per day.

[0140] In some embodiments, the daily dosage of azacitidine for a human subject may be about 5 to about 200 mg, about 20 to about 192 mg, about 40 to about 180 mg, about 60 to about 172 mg, about 80 to about 160 mg, about 100 to about 160 mg, about 120 to about 160 mg, or about 136 to about 144 mg per day. In some embodiments, the daily dosage of azacitidine for a human subject may be about 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, or 160 mg per day.

[0141] The compositions of the present application may be administered once, twice, three, or four times daily, using any suitable mode described above. Also, administration or treatment with the compounds may be continued for a number of days; for example, commonly treatment would continue for at least 7 days, 14 days, or 28 days, for one cycle of treatment. Treatment cycles are well known in cancer chemotherapy, and are frequently alternated with resting periods of about 1 to 28 days, commonly about 7 days or about 14 days, between cycles. The treatment cycles, in other embodiments, may also be continuous.

Fixed Dose Combination (Immediate Release Cedazuridine + Modified Release Azacitidine)

[0142] In some embodiments, a fixed dose combination, a pharmaceutical dosage form or a composition comprises cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a pharmaceutically acceptable salt thereof, wherein at least a portion of the azacitidine is formulated for modified release and at least a portion of the cedazuridine is formulated for immediate release. In some embodiments, a fixed dose combination, a pharmaceutical dosage form or a composition comprises cedazuridine or a pharmaceutically acceptable salt thereof, and azacitidine or a pharmaceutically acceptable salt thereof, wherein at least a portion of the azacitidine is formulated for modified release and all or substantially all of the cedazuridine is formulated for immediate release. In some embodiments, a fixed dose combination, a pharmaceutical dosage form or a composition comprises cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a pharmaceutically acceptable salt thereof, wherein all or substantially all of the azacitidine is formulated for modified release and at least a portion of the cedazuridine is formulated for immediate release.

[0143] In some embodiments, a fixed dose combination, a pharmaceutical dosage form or a composition comprises cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a

pharmaceutically acceptable salt thereof, wherein the azacitidine is formulated for modified release and the cedazuridine is formulated for immediate release. The azacitidine formulated for modified release may be coated. In some embodiments, the coated azacitidine is in the form of pellets or minitabets. In some of such embodiments, the cedazuridine formulated for immediate release is uncoated. In some embodiments the uncoated cedazuridine is a powder. In some embodiments, the uncoated cedazuridine is a blend (e.g., powder blend). In some embodiments, the uncoated cedazuridine is in the form of granules. In some embodiments, the uncoated cedazuridine is in the form of pellets. In some embodiments the uncoated cedazuridine is in the form of minitabets. Each of the cedazuridine and the azacitidine may be formulated according to the following description. For example, the fixed dose combination, pharmaceutical dosage form or composition includes cedazuridine in a form of uncoated minitabets or pellets described herein, and azacitidine in a form of minitabets or pellets coated for modified release described herein. The fixed dose combination may be provided in a form of capsule.

Cedazuridine Formulation

[0144] The cedazuridine in the fixed dose combination, pharmaceutical dosage form or composition may be formulated such that the effect of enhancing azacitidine bioavailability is achieved. The cedazuridine in the fixed dose combination, pharmaceutical dosage form or composition may be in the form of a minitab, tablet, powder, a blend, granules, or pellets, and may further include lactose monohydrate, a filler, a binder, a disintegrant, a glidant, and/or a lubricant. In some embodiments, the pharmaceutical dosage form of cedazuridine (i.e. cedazuridine minitabets, tablet, powder, blend, granules, or pellets) comprises about 10%-90% w/w, about 10%-80% w/w, about 10%-60% w/w, or about 10%-40% w/w of cedazuridine, about 50%-90% w/w of cedazuridine, about 60%-90% w/w of cedazuridine, about 50%-85% w/w of cedazuridine, about 60%-85% w/w of cedazuridine, about 70%-90% w/w of cedazuridine, about 70%-85% w/w of cedazuridine, about 75%-85% w/w of cedazuridine, about 75%-80% w/w of cedazuridine, about 80%-85% w/w of cedazuridine, about 80%-90% w/w of cedazuridine, or about 70%-80% w/w of cedazuridine, about 15%-40% w/w of cedazuridine, about 25%-40% w/w of cedazuridine, about 20%-40% w/w of cedazuridine, about 30%-40% w/w of cedazuridine, about 15%-35% w/w of cedazuridine, about 15%-30% w/w of cedazuridine, or about 20%-30% w/w of cedazuridine, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine minitabets, tablet, powder, blend, granules, or pellets.

[0145] In some embodiments, the cedazuridine is in the form of one or more tablets, minitabets or pellets. For example, the fixed dose combination, pharmaceutical dosage form or composition may comprise azacitidine or pharmaceutically acceptable salt thereof, and cedazuridine or pharmaceutically acceptable salt thereof, wherein the cedazuridine is in the form of one or more tablets, minitabets or pellets, and cedazuridine tablets, minitabets or pellets may comprise about 10%-40% w/w of cedazuridine, about 10%-30% w/w, about 15%-40% w/w, about 15%-30% w/w, or about 15%-25% w/w of cedazuridine wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine tablets, minitabets or pellets. In some embodiments, the cedazuridine tablets, minitabets,

or pellets further comprise about 40%-80% w/w of lactose monohydrate, about 0.5-10% w/w of hydroxypropyl methylcellulose (HPMC), about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine tablets, minitables, or pellets. In some embodiments, the cedazuridine pellet or minitabulet comprise about 10%-30% w/w of cedazuridine, 40%-80% w/w of lactose monohydrate, about 0.5-10% w/w of hydroxypropyl methylcellulose (HPMC), about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine tablets, minitables, or pellets. In some embodiments, the cedazuridine tablets, minitables, or pellets comprise about 20% w/w of cedazuridine, about 71.5% w/w of lactose monohydrate, about 2% w/w of hydroxypropyl methylcellulose (HPMC), about 5% w/w of croscarmellose sodium, about 1.0% w/w of silicon dioxide, and about 0.5% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine tablets, minitables, or pellets.

[0146] In some embodiments, the cedazuridine is in the form of powder, blend, or granules. For example, the fixed dose combination, pharmaceutical dosage form or composition may comprise azacitidine or pharmaceutically acceptable salt thereof, and cedazuridine or pharmaceutically acceptable salt thereof, wherein the cedazuridine is in the form of powder or granules, and the cedazuridine powder or granules may comprise about 70%-90% w/w of cedazuridine, about 70%-85% w/w of cedazuridine, about 75%-90% w/w of cedazuridine, or about 75%-85% w/w of cedazuridine, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine powder or granules. The cedazuridine powder or granules may further comprise about 10%-20% w/w of lactose monohydrate, about 1%-10.5% w/w of croscarmellose sodium, about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine powder or granules. In some embodiments, the cedazuridine powder or granule comprises about 80% w/w of cedazuridine, 13.5% w/w of lactose monohydrate, about 5% w/w of croscarmellose sodium, about 1.0% w/w of silicon dioxide, and about 0.5% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine powder or granule.

Azacitidine Formulation

[0147] The azacitidine in the fixed dose combination, pharmaceutical dosage form or composition may be formulated such that the azacitidine bioavailability is enhanced. In some embodiments of the fixed dose combination, pharmaceutical dosage form, or pharmaceutical composition, the azacitidine is provided as minitables or pellets. Uncoated azacitidine minitables or pellets form cores which are optionally coated with release modifying coatings. In some embodiments of the pharmaceutical dosage form, the portion of azacitidine that is formulated for modified release is provided as enteric-coated minitables or pellets. In some embodiments, the enteric coating, or the release modifying coating is pH sensitive.

[0148] The azacitidine minitablets or pellets includes azacitidine and one or more pharmaceutically acceptable excipients, such as lactose monohydrate, a filler, a binder, a disintegrant, a glidant, and/or a lubricant. The azacitidine minitablets or pellets of azacitidine may comprise about 10%-70% w/w, about 10%-60% w/w, about 10%-50% w/w, about 10%-40% w/w, about 15%-40% w/w, about 20%-40% w/w, about 25%-40% w/w, about 30%-40% w/w, about 20%-60% w/w, about 25%-50% w/w, about 25%-45% w/w, about 30%-45% w/w, about 20%-60% w/w, about 20%-50% w/w, about 30%-50% w/w, or about 35%-45% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated minitablets or pellets. In some embodiments, the azacitidine minitablets or pellets comprises about 40% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets.

[0149] In some embodiments, the azacitidine minitablets or pellets includes about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, or 6 mg of azacitidine.

[0150] In some embodiments, the pharmaceutical dosage form comprises about 10%-60% w/w of lactose monohydrate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 10%-50% w/w, about 10%-40% w/w, about 10%-30% w/w, or about 10%-20% w/w, of lactose monohydrate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 10% -60% w/w of microcrystalline cellulose, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 10% -50% w/w, about 20% -40% w/w, or about 20% -30% w/w of microcrystalline cellulose, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 0.5-10% w/w of hydroxypropyl methylcellulose (HPMC), wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 0.5-8% w/w, about 0.5-6% w/w, about 0.5-4% w/w, or about 1-4% w/w of hydroxypropyl methylcellulose (HPMC), wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 1%-10% w/w of croscarmellose sodium, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 1%-8% w/w, about 2%-8% w/w, or about 3%-6% w/w of croscarmellose sodium, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 0.1%-3% w/w of silicon dioxide, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 0.1%-2% w/w, or about 0.5%-2% w/w of silicon dioxide, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 0.1%-3% w/w of magnesium stearate,

wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the pharmaceutical dosage form comprises about 0.1%-2% w/w, or about 0.1%-1% of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets.

[0151] In some embodiments, the azacitidine minitablets or pellets comprise about 20%-50% w/w of azacitidine, about 10%-60% w/w of lactose monohydrate, about 2%-50% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.5%-10% w/w of hydroxypropyl methylcellulose (HPMC), about 0.1%-4% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the azacitidine minitablets or pellets comprise about 40% w/w of azacitidine, about 19.7% w/w of lactose monohydrate, about 30% w/w of microcrystalline cellulose, about 5% w/w of croscarmellose sodium, about 2% w/w of hydroxypropyl methylcellulose (HPMC), about 2.1% w/w of silicon dioxide, and about 1.2% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets.

[0152] In some embodiments of the fixed dose combination, pharmaceutical dosage form or composition the azacitidine uncoated minitablets or pellets comprise one or more layers. For example, the azacitidine uncoated minitablets or pellets comprise one or more layers may comprise an intragranular layer and an extragranular layer.

[0153] In some embodiments the intragranular layer comprises about 70%-92% w/w of azacitidine minitablets or pellets, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the intragranular layer comprises about 70%-95% w/w, about 75%-95% w/w, about 80%-95% w/w, about 85%-95% w/w, or about 90%-92% of azacitidine minitablets or pellets, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments the intragranular layer comprises about 90.5% w/w of azacitidine minitablets or pellets, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets.

[0154] In some embodiments, in each uncoated minitablet or pellet, the intragranular layer comprises about 20%-50% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the intragranular layer comprises about 20%-60% w/w, about 25%-50% w/w, about 25%-45% w/w, about 30%-45% w/w, or about 35%-45% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the intragranular layer comprises about 10%-60% w/w of lactose monohydrate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the intragranular layer comprises about 10%-40% w/w, about 10%-30% w/w, or about 15%-25% w/w, of lactose monohydrate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the intragranular layer comprises about 2%-50% w/w of microcrystalline cellulose,

wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 2%-40% w/w, about 5%-40% w/w, about 10%-40% w/w, about 15%-30% w/w or about 20%-30% w/w of microcrystalline cellulose, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 1%-10% w/w of croscarmellose sodium, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 1%-10% w/w, about 1%-8% w/w, about 1%-6% w/w, or about 1%-4% w/w of croscarmellose sodium, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 0.5%-10% w/w of hydroxypropyl methylcellulose (HPMC), wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 0.5%-8% w/w, about 0.5%-6% w/w, about 0.5%-4% w/w, or about 1%-4% w/w of hydroxypropyl methylcellulose (HPMC), wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 0.1%-3% w/w of silicon dioxide, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 0.1%-2% w/w, or about 0.1%-1% w/w of silicon dioxide, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 0.1%-2% w/w, or about 0.1%-1% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets.

[0155] In some embodiments, the intragranular layer comprises about 20%-50% w/w of azacitidine, about 10%-60% w/w of lactose monohydrate, about 2%-50% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.5%-10% w/w of hydroxypropyl methylcellulose (HPMC), about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the intragranular layer comprises about 40% w/w of azacitidine, about 19.7% w/w of lactose monohydrate, about 25% w/w of microcrystalline cellulose, about 2.5% w/w of croscarmellose sodium, about 2% w/w of HPMC, about 0.5% w/w of silicon dioxide, and about 0.8% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets.

[0156] In some embodiments, the extragranular layer comprises about 1%-60% w/w of microcrystalline cellulose, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some embodiments, the extragranular layer comprises about 1%-50% w/w, about 1%-40% w/w, about 1%-30%, about 1%-20% w/w, or about 1%-10% w/w of

microcrystalline cellulose, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 1%-10% w/w of croscarmellose sodium, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 1%-8% w/w, about 1%-6% w/w, about 1%-4% w/w or about 2%-4% w/w of croscarmellose sodium, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 0.1%-3% w/w silicon dioxide, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 0.1%-2% w/w silicon dioxide, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 0.1%-2% w/w, or about 0.1%-1% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets.

[0157] In some embodiments, the extragranular layer comprises about 1%-60% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the extragranular layer comprises about 5% w/w of microcrystalline cellulose, about 2.5% w/w of croscarmellose sodium, about 1.6% w/w silicon dioxide, and about 0.4% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets.

[0158] In some embodiments of the fixed dose combination, pharmaceutical dosage form or composition the azacitidine uncoated minitablets or pellets comprise the extragranular layer and the intragranular layer, wherein the intragranular layer comprises about 20%-50% w/w of azacitidine, about 10%-60% w/w of lactose monohydrate, about 2%-50% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.5%-10% w/w of hydroxypropyl methylcellulose (HPMC), about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, and wherein the extragranular layer comprises about 1%-60% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets or pellets. In some embodiments, the intragranular layer comprises about 40% w/w of azacitidine, about 19.7% w/w of lactose monohydrate, about 25% w/w of microcrystalline cellulose, about 2.5% w/w of croscarmellose sodium, about 2% w/w of HPMC, about 0.5% w/w of silicon dioxide, and about 0.8% w/w of magnesium stearate, and the extragranular layer comprises about 5% w/w of microcrystalline cellulose, about 2.5% w/w of croscarmellose sodium, about 1.6% w/w silicon dioxide,

and about 0.4% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitables or pellets.

[0159] In some embodiments of the fixed dose combination, pharmaceutical dosage form or composition the azacitidine uncoated minitables or pellets comprise the extragranular layer and the intragranular layer, wherein the intragranular layer comprises about 20%-50% w/w of azacitidine, about 10%-30% w/w of lactose monohydrate, about 2%-50% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.5%-10% w/w of hydroxypropyl methylcellulose (HPMC), about 0.1%-3% w/w of silicon dioxide, about 0.5%-5% w/w of binder (e.g. Kollidon VA64), and about 0.1%-3% w/w of magnesium stearate, and wherein the extragranular layer comprises about 1%-60% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitables or pellets. The extragranular layer comprises about 2%-10% w/w of microcrystalline cellulose, about 1%-5% w/w of croscarmellose sodium, about 0.1%-1% w/w of magnesium stearate, and about 1%-5% of binder (e.g., Kollidon VA64).

[0160] In some embodiments, the azacitidine minitab or pellet is not separated into two layers, and comprises about 2%-10% w/w of azacitidine, about 50%-90% w/w of lactose monohydrate, about 2%-10% w/w of croscarmellose sodium, about 1-5% w/w of HPMC, about 0.1%-3% of colloidal silicon dioxide, and 0.1%-3% of magnesium stearate.

Coating

[0161] In some embodiments of the fixed dose combination, pharmaceutical dosage form, or composition, the azacitidine that is formulated for modified release comprises azacitidine minitables or pellets described herein, coated with one or more layers to enable enteric release. In some embodiments of the fixed dose combination, pharmaceutical dosage form, or composition, the azacitidine that is formulated for modified release comprises azacitidine uncoated minitables or pellets described herein, coated with one or more layers of a seal coat. In some embodiments, the minitables or pellets coated with the seal coat are further coated with a second seal coat, or an intermediate coat. In some embodiments, the minitables or pellets coated with the seal coat and the second seal coat are further coated with an enteric coating, modified release coating, or delayed release coating, providing a 3-layer coating. By way of example only, Examples 4 and 5 illustrate such an embodiment. In some embodiments of the fixed dose combination, the minitables or pellets may be coated with a seal coat, and an enteric coating or modified release coating, providing a 2-layer coating.

[0162] In some embodiments, the seal coat or the second seal coat comprises ingredients to protect the core, such as hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), magnesium oxide or other ingredients suitable for a seal coat for a drug.

[0163] The enteric coating or modified release coating comprises ingredients to protect the core minitables or pellets through the acidity of stomach, and allow release in the small intestine. In some embodiments, the delayed release coating comprises ethyl cellulose, or ethyl cellulose-based polymer.

For example, the delayed release coating comprises Surelease® E-7-19040. In some embodiments, the delayed release coating is insensitive to pH variations in the intestine. In some of such embodiments, the azacitidine is released outside the stomach.

[0164] In some embodiments of the fixed dose combination, pharmaceutical dosage form, or the composition, the enteric or delayed release coating comprises methacrylate-based polymers. In some embodiments, the enteric or delayed release coating may include Eudragit® L30D 55, FS 30 D, FL 30 D-55, or L100. In some embodiments, the enteric or delayed release coating may include methyl methacrylate-methacrylic acid copolymers, hydroxypropyl methylcellulose acetate succinates, cellulose acetate phthalate, cellulose acetate succinate, polyvinyl acetate phthalate, or a copolymer thereof. The enteric or delayed release coating may further include triethyl citrate and/or talc. In some embodiments, the enteric delayed release coating is sensitive to pH variations in the intestine. In some of such embodiments, depending on the polymer present in the coating, the enteric or delayed release coating is chosen to provide release in the duodenum, the jejunum, the ileum, or the colon. In some of such embodiments, the azacitidine is released outside the stomach. By way of example only, Example 6 illustrates such an embodiment.

[0165] The coating for the azacitidine minitablets or pellets may be applied in an amount suitable for providing desired release profile. In some embodiments, the total coating for the azacitidine minitablets or pellets may have weight gains of about 5-25%, about 10-25%, about 15-25%, about 20-25%, about 5-20%, about 10-20%, about 15-20%, about 5-15%, about 10-15%, or about 5-10% compared to uncoated azacitidine minitablets or pellets. In some embodiments, the enteric or delayed release coating for the azacitidine minitablets or pellets may have weight gains of about 3-15%, about 3-12%, about 3-10%, about 4-10%, or about 4-7%, compared to uncoated azacitidine minitablets or pellets.

Fixed Dose Combination Embodiments

[0166] In some or any of the preceding embodiments, provided herein is a fixed dose combination, pharmaceutical dosage form, or pharmaceutical composition comprising cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a pharmaceutically acceptable salt thereof, wherein the cedazuridine is formulated for immediate release and provided as powder, granules, pellets or minitablets; and all of the azacitidine is formulated for modified release and provided as enteric-coated minitablets or pellets. The fixed dose combination may be provided as a capsule.

[0167] In some of such embodiments, the azacitidine minitablets or pellets comprise an intragranular layer and an extragranular layer. The intragranular layer comprises about 20%-50% w/w of azacitidine, about 10%-60% w/w of lactose monohydrate, about 2%-50% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.5%-10% w/w of hydroxypropyl methylcellulose (HPMC), about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate. The extragranular layer comprises about 1%-60% w/w of microcrystalline cellulose, about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine

minitabets or pellets. In some of such embodiments, the intragranular layer comprises about 40% w/w of azacitidine, about 19.7% w/w of lactose monohydrate, about 25% w/w of microcrystalline cellulose, about 2.5% w/w of croscarmellose sodium, about 2% w/w of HPMC, about 0.5% w/w of silicon dioxide, and about 0.8% w/w of magnesium stearate, and the extragranular layer comprises about 5% w/w of microcrystalline cellulose, about 2.5% w/w of croscarmellose sodium, about 1.6% w/w silicon dioxide, and about 0.4% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitabets or pellets. In some of such embodiments, the azacitidine minitabets or pellets are coated with a seal coat and an enteric or modified release coat. The enteric or modified release coat comprises polymethacrylate based polymers, and is sensitive to pH in intestine. The azacitidine is substantially released outside the stomach.

[0168] In some of such embodiments, the cedazuridine is provided as pellets or minitabets and the cedazuridine pellets or minitabets comprise about 10%-30% w/w of cedazuridine, 40%-80% w/w of lactose monohydrate, about 0.5-10% w/w of hydroxypropyl methylcellulose (HPMC), about 1%-10% w/w of croscarmellose sodium, about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine tablets, minitabets, or pellets. In some of such embodiments, the cedazuridine tablets, minitabets, or pellets comprise about 20% w/w of cedazuridine, about 71.5% w/w of lactose monohydrate, about 2% w/w of hydroxypropyl methylcellulose (HPMC), about 5% w/w of croscarmellose sodium, about 1.0% w/w of silicon dioxide, and about 0.5% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine tablets, minitabets, or pellets.

[0169] In other of such embodiments, the cedazuridine is in the form of powder, and the cedazuridine powder may comprise about 70%-90% w/w of cedazuridine, about 10%-20% w/w of lactose monohydrate, about 1%-10.5% w/w of croscarmellose sodium, about 0.1%-3% w/w of silicon dioxide, and about 0.1%-3% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine powder or granules. In some embodiments, the cedazuridine powder or granule comprises about 80% w/w of cedazuridine, 13.5% w/w of lactose monohydrate, about 5% w/w of croscarmellose sodium, about 1.0% w/w of silicon dioxide, and about 0.5% w/w of magnesium stearate, wherein the percentage by weight is relative to the total weight of the uncoated cedazuridine powder or granule.

[0170] In some or any of the preceding embodiments, provided herein is a pharmaceutical dosage form comprising cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a pharmaceutically acceptable salt thereof, wherein the cedazuridine is formulated for immediate release; at least a portion of the azacitidine is formulated for immediate release and provided as uncoated minitabets or pellets, and the remainder of the azacitidine is formulated for modified release and provided as enteric-coated minitabets or pellets. In some of such embodiments, the azacitidine minitabets or pellets are uniform (i.e., do not comprise intragranular and extragranular layers). In some

other of such embodiments, the azacitidine minitabets or pellets comprise an intragranular layer and an extragranular layer.

[0171] In some or any of the preceding embodiments, provided herein is a pharmaceutical dosage form comprising cedazuridine, or a pharmaceutically acceptable salt thereof, and azacitidine, or a pharmaceutically acceptable salt thereof, wherein the cedazuridine is formulated for immediate release; and all of the azacitidine is formulated for modified release and provided as delayed-release minitabets or pellets. In some of such embodiments, the azacitidine pellets comprise an intragranular layer and an extragranular layer. In some other of such embodiments, the azacitidine pellets are uniform (i.e., do not comprise intragranular and extragranular layers).

Treatment Methods and Uses

[0172] “Treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (*e.g.*, metastasis) of the disease or condition); and/or c) relieving the disease, that is, causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival).

[0173] “Prevention” or “preventing” means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[0174] “Subject” refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation, or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In one embodiment, the subject is a human.

[0175] The term “therapeutically effective amount” or “effective amount” of a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. For example, a therapeutically effective amount may be an amount sufficient to decrease a symptom of cancer. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art.

[0176] Provided herein is a method of treating cancer in a patient comprising administering any dosage form described herein to the patient in need thereof.

[00100] Examples of types of cancers which can be treated herein include, but are not limited to, solid tumors such as glandular tumors, carcinoid tumors, undifferentiated carcinomas, angiosarcoma, adenocarcinoma, gastrointestinal cancers (e.g., colorectal cancers (“CRC”) including colon cancer, rectal cancer, and cecal cancer, biliary cancers including gall bladder cancer and bile duct cancer (cholangiocarcinoma), anal cancer, esophageal cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor(s), gastrointestinal stromal tumor(s) (“GIST”), liver cancer, duodenal cancer, appendiceal cancer, and small intestine cancer), lung cancers (e.g., non-small cell lung cancer (“NSCLC”), squamous-cell lung carcinoma, large-cell lung carcinoma, small cell lung carcinoma, invasive mucinous adenocarcinoma, mesothelioma and other lung cancers such as bronchial tumors and pleuropulmonary blastoma), urological cancers (e.g., kidney (renal) cancer, transitional cell cancer (“TCC”) of kidney, TCC of the renal pelvis and ureter (“PDQ”), bladder cancer, urethral cancer and prostate cancer), head and neck cancers (e.g., eye cancer, retinoblastoma, intraocular melanoma, hypopharyngeal cancer, pharyngeal cancer, laryngeal cancer, laryngeal papillomatosis, metastatic squamous neck cancer with occult primary, sinonasal squamous cell carcinoma (SNSCC), oral (mouth) cancer, lip cancer, throat cancer, oropharyngeal cancer, esthesioneuroblastoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, and salivary gland cancer), endocrine cancers (e.g., thyroid cancer, parathyroid cancer, multiple endocrine neoplasia syndromes, thymoma and thymic carcinoma, pancreatic cancers including pancreatic ductal adenocarcinoma (“PDAC”), pancreatic neuroendocrine tumors and islet cell tumors), breast cancers (extrahepatic ductal carcinoma in situ (“DCIS”), lobular carcinoma in situ (“LCIS”), triple negative breast cancer, and inflammatory breast cancer), male and female reproductive cancers (e.g., cervical cancer, ovarian cancer, endometrial cancer, uterine sarcoma, uterine cancer, vaginal cancer, vulvar cancer, gestational trophoblastic tumor (“GTD”), extragonadal germ cell tumor, extracranial germ cell tumor, germ cell tumor, testicular cancer and penile cancer), brain and nervous system cancers (e.g., astrocytomas, brain stem glioma, brain tumor, glioblastoma (GBM), craniopharyngioma, central nervous system (“CNS”) cancer, chordomas, ependymoma, embryonal tumors, neuroblastoma, paraganglioma, atypical teratoid, oligodendroma, oligodendroastrocytoma, oligodendroglioma, anaplastic oligodendroastrocytoma, ganglioglioma, central neurocytoma, medulloblastoma, germinoma, meningioma, neurilemmoma, GH secreting pituitary adenoma, PRL-secreting pituitary adenoma, ACTH-secreting pituitary adenoma, nonfunctional pituitary adenoma, hemangioblastoma, and epidermoid tumor), skin cancers (e.g., basal cell carcinoma (“BCC”), squamous cell skin carcinoma (“SCC”), Merkel cell carcinoma and melanoma), tissue and bone cancers (e.g., soft-tissue sarcoma, rhabdomyosarcoma, fibrous histiocytoma of bone, Ewing sarcoma, malignant fibrous histiocytoma of bone (“MFH”), osteosarcoma and chondrosarcoma), cardiovascular cancers (e.g., heart cancer and cardiac tumors), appendix cancers, childhood and adolescent cancers (e.g., adrenocortical carcinoma childhood, midline tract carcinoma, hepatocellular carcinoma (“HCC”),

hepatoblastoma and Wilms' tumor) and viral-induced cancers (e.g., HHV-8 related cancers (Kaposi sarcoma) and HIV/AIDS related cancers).

[00101] Cancers also suitable for treatment may include, but are not limited to, hematological and plasma cell malignancies (e.g., cancers that affect blood, bone marrow and/or lymph nodes) such as multiple myeloma, leukemias and lymphomas, myelodysplastic syndromes and myeloproliferative disorders. Leukemias include, without limitation, acute lymphoblastic leukemia ("ALL"), acute myelogenous (myeloid) leukemia ("AML"), chronic lymphocytic leukemia ("CLL"), chronic myelogenous leukemia ("CML"), acute monocytic leukemia ("AMoL"), hairy cell leukemia, and/or other leukemias. Lymphomas include, without limitation, Hodgkin's lymphoma and non-Hodgkin's lymphoma ("NHL"). In some embodiments, NHL is B-cell lymphomas and/or T-cell lymphomas. In some embodiments, NHL includes, without limitation, diffuse large B-cell lymphoma ("DLBCL"), small lymphocytic lymphoma ("SLL"), chronic lymphocytic leukemia ("CLL"), mantle cell lymphoma ("MCL"), Burkitt's lymphoma, cutaneous T-cell lymphoma including mycosis fungoides and Sézary syndrome, AIDS-related lymphoma, follicular lymphoma, lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia ("WM")), primary central nervous system (CNS) lymphoma, central nervous system malignant lymphoma, and/or other lymphomas.

[0177] In some embodiments, the cancer is selected from hematological cancers and solid cancers. In further embodiments, the hematological cancer is selected from myelodysplastic syndromes (MDS) and leukemia. In further embodiments, the solid cancer is selected from pancreatic cancer, ovarian cancer, prostate cancer, peritoneal cancer, non-small cell lung cancer, and breast cancer. In yet further embodiments, the leukemia is acute myeloid leukemia (AML) or chronic myeloid leukemia (CML). In some embodiments, the AML may be relapsed or refractory AML. In some embodiments, the AML may be before or after hematopoietic cell transplant. In some embodiments, the cancer is mucosal melanoma. In some embodiments, the leukemia is recurrent or refractory acute biphenotypic leukemia. In some embodiments, the AML patients may have achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

[0178] In some embodiments, the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML or CMMoL), previously treated or untreated, de novo or secondary chronic myelogenous leukemia (CML), and previously treated or untreated, de novo or secondary juvenile myelomonocytic leukemia (JMML). In some embodiments, the MDS may be with intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

[0179] In some embodiments, the cancer is associated with refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T).

[0180] In some embodiments, the cancer is selected from malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer,

primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.

[0181] In some embodiments, the patient has moderate or severe hepatic impairment. In some embodiments, the patient has normal hepatic function.

[0182] In some embodiments, the patient has moderate or severe renal impairment. In some embodiments, the patient has normal renal function.

[0183] In some embodiments, the pharmaceutical dosage form described herein may be administered orally. In some embodiments, the pharmaceutical dosage form described herein may be administered once, twice, or three times a day. In some embodiments, the pharmaceutical dosage form described herein may be administered once a day, or once in 2, 3, 4, 5, 6, or 7 days. In some embodiments, the pharmaceutical dosage form described herein may be administered by cycle. For example, the pharmaceutical dosage form described herein may be administered for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 days in each cycle.

[0184] Also provided is a pharmaceutical dosage form described herein for use in treating cancer.

Combination Therapy

[0185] In one embodiment, the compounds, pharmaceutical compositions, and/or dosage forms disclosed herein may be used in combination with one or more additional therapeutic agents that are being used and/or developed to treat cancers, T-cell lymphomas, such as bone marrow / stem cell transplant and/or CAR T cell therapies. In some embodiments, the pharmaceutical composition or a dosage form described herein may include one or more anti-cancer agents in addition to azacitidine and cedazuridine.

[0186] The different agents may be administered sequentially or simultaneously (in separate compositions or in the same composition). Useful classes of agents for combination therapy include, but are not limited to kinase inhibitors, CDA inhibitors, Anti-PD-1 monoclonal antibody.

[0187] In some embodiments, the one or more additional therapeutic agent may be tolinapant or venetoclax. In some embodiments, a dosage form may include tolinapant and/or venetoclax in addition to azacitidine and cedazuridine.

[0188] In some embodiments, the pharmaceutical composition including azacitidine and cedazuridine, may be administered in combination with other therapeutic agents.

[0189] Examples of anticancer agents include, but are not limited to, chemotherapeutic agents (e.g., cytotoxic agents), immunotherapeutic agents, hormonal and anti-hormonal agents, targeted therapy agents, and anti-angiogenesis agents. Many anti-cancer agents can be classified within one or more of these groups. While certain anticancer agents have been categorized within a specific group(s) or subgroup(s) herein, many of these agents can also be listed within one or more other group(s) or subgroup(s), as would be presently understood in the art. The anticancer agent is not particularly limited, and examples thereof include, but are not limited to, a chemotherapeutic agent, a mitotic inhibitor, a plant

alkaloid, an alkylating agent, an anti-metabolite, a platinum analog, an enzyme, a topoisomerase inhibitor, a retinoid, an aziridine, an antibiotic, a hormonal agent, an anti-hormonal agent, an anti-estrogen, an anti-androgen, an anti-adrenal, an androgen, a targeted therapy agent, an immunotherapeutic agent, a biological response modifier, a cytokine inhibitor, a tumor vaccine, a monoclonal antibody, an immune checkpoint inhibitor, an anti-PD-1 agent, an anti-PD-L1 agent, an anti-TIGIT agent, a colony-stimulating factor, an immunomodulator, an immunomodulatory imide (IMiD), an anti-CTLA4 agent, an anti-LAG1 agent, an anti-OX40 agent, a GITR agonist, a CAR-T cell, a BiTE, a signal transduction inhibitor, a growth factor inhibitor, a tyrosine kinase inhibitor, an EGFR inhibitor, a HER2 inhibitor, a histone deacetylase (HDAC) inhibitor, a proteasome inhibitor, a cell-cycle inhibitor, an anti-angiogenesis agent, a matrix-metalloproteinase (MMP) inhibitor, a hepatocyte growth factor inhibitor, a TOR inhibitor, a KDR inhibitor, a VEGF inhibitor, a HIF-1 α inhibitor, a HIF-2 α inhibitor, a fibroblast growth factor (FGF) inhibitor, a RAF inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, an AKT inhibitor, an MCL-1 inhibitor, a BCL-2 inhibitor, an SHP2 inhibitor, a BRAF-inhibitor, a RAS inhibitor, a gene expression modulator, an autophagy inhibitor, an apoptosis inducer, an antiproliferative agent, and a glycolysis inhibitor.

[0190] Non-limiting examples of chemotherapeutic agents include mitotic inhibitors and plant alkaloids, alkylating agents, anti-metabolites, platinum analogs, enzymes, topoisomerase inhibitors, retinoids, aziridines, and antibiotics.

[0191] Non-limiting examples of mitotic inhibitors and plant alkaloids include taxanes such as cabazitaxel, docetaxel, larotaxel, ortataxel, paclitaxel, and tesetaxel; demecolcine; epothilone; eribulin; etoposide (VP- 16); etoposide phosphate; navelbine; noscapine; teniposide; thaliblastine; vinblastine; vincristine; vindesine; vinflunine; and vinorelbine.

[0192] Non-limiting examples of alkylating agents include nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, cytophosphane, estramustine, ifosfamide, mannomustine, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, tris(2-chloroethyl)amine, trofosfamide, and uracil mustard; alkyl sulfonates such as busulfan, improsulfan, and piposulfan; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, streptozotocin, and TA-07; ethylenimines and methylamelamines such as altretamine, thiotepa, triethylenemelamine, triethylenethiophosphaoramide, triethylenephosphoramidate, and trimethylolomelamine; ambamustine; bendamustine; dacarbazine; cyclophosphamide; etoglucid; irofulven; mafosfamide; mitobronitol; mitolactol; pipobroman; procarbazine; temozolomide; treosulfan; and triaziquone.

[0193] Non-limiting examples of anti-metabolites include folic acid analogues such as aminopterin, denopterin, edatrexate, methotrexate, pteropterin, raltitrexed, and trimetrexate; purine analogs such as 6-mercaptopurine, 6-thioguanine, fludarabine, forodesine, thiamiprine, and thioguanine; pyrimidine analogs such as 5-fluorouracil (5-FU), tegafur/gimeracil/oteracil potassium, tegafur/uracil, trifluridine, trifluridine/tipiracil hydrochloride, 6-azauridine, ancitabine, azacytidine, capecitabine, carmofur, cytarabine, decitabine, dideoxyuridine, doxifluridine, doxifluridine, enocitabine, floxuridine,

galocitabine, gemcitabine, and sapacitabine; 3-aminopyridine-2-carboxaldehyde thiosemicarbazone; broxuridine; cladribine; cyclophosphamide; cytarabine; emitefur; hydroxyurea; mercaptopurine; nelarabine; pemetrexed; pentostatin; tegafur; and troxacitabine.

[0194] Non-limiting examples of platinum analogs include carboplatin, cisplatin, dicycloplatin, heptaplatin, lobaplatin, nedaplatin, oxaliplatin, satraplatin, and triplatin tetranitrate.

[0195] Non-limiting examples of enzymes include asparaginase and pegaspargase.

[0196] Non-limiting examples of topoisomerase inhibitors include acridine carboxamide, amonafide, amsacrine, belotecan, elliptinium acetate, exatecan, indolocarbazole, irinotecan, lurtotecan, mitoxantrone, razoxane, rubitecan, SN-38, sobuzoxane, and topotecan.

[0197] Non-limiting examples of retinoids include alitretinoin, bexarotene, fenretinide, isotretinoin, liarozole, RII retinamide, and tretinoin.

[0198] Non-limiting examples of aziridines include benzodopa, carboquone, meturedopa, and uredopa.

[0199] Non-limiting examples of antibiotics include intercalating antibiotics; anthracenediones; anthracycline antibiotics such as aclarubicin, amrubicin, daunomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, nogalamycin, pirarubicin, and valrubicin; 6-diazo-5-oxo- L-norleucine; aclacinomysins; actinomycin; authramycin; azaserine; bleomycins; cactinomycin; calicheamicin; carabycin; carminomycin; carzinophilin; chromomycins; dactinomycin; detorubicin; esorubicin; esperamicins; geldanamycin; marcellomycin; mitomycins; mitomycin C; mycophenolic acid; olivomycins; novantrone; peplomycin; porfiromycin; potfiromycin; puromycin; quelamycin; rebeccamycin; rodorubicin; streptonigrin; streptozocin; tanespimycin; tubercidin; ubenimex; zinostatin; zinostatin stimalamer; and zorubicin.

[0200] Non-limiting examples of hormonal and anti-hormonal agents include anti-androgens such as abiraterone, apalutamide, bicalutamide, darolutamide, enzalutamide, flutamide, goserelin, leuprolide, and nilutamide; anti-estrogens such as 4-hydroxy tamoxifen, aromatase inhibiting 4(5)-imidazoles, EM-800, fosfestrol, fulvestrant, keoxifene, LY 117018, onapristone, raloxifene, tamoxifen, toremifene, and trioxifene; anti-adrenals such as aminoglutethimide, dexaminoglutethimide, mitotane, and trilostane; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitiostane, and testolactone; abarelix; anastrozole; cetrorelix; deslorelin; exemestane; fadrozole; finasteride; formestane; histrelin (RL 0903); human chorionic gonadotropin; lanreotide; LDI 200 (Milkhaus); letrozole; leuprorelin; mifepristone; nafarelin; nafoxidine; osaterone; prednisone; thyrotropin alfa; and triptorelin.

[0201] Non-limiting examples of immunotherapeutic agents (i.e., immunotherapy) include biological response modifiers, cytokine inhibitors, tumor vaccines, monoclonal antibodies, immune checkpoint inhibitors, colony-stimulating factors, and immunomodulators.

[0202] Non-limiting examples of biological response modifiers, including cytokine inhibitors (cytokines) such as interferons and interleukins, include interferon alfa/interferon alpha such as interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon alfacon-1, peginterferon alfa-2a, peginterferon alfa-2b, and leukocyte alpha interferon; interferon beta such as

interferon beta-1a, and interferon beta-1b; interferon gamma such as natural interferon gamma-1a, and interferon gamma-1b; aldesleukin; interleukin-1 beta; interleukin-2; oprelvekin; sonermin; tasonermin; and virulizin.

[0203] Non-limiting examples of tumor vaccines include APC 8015, AVICINE, bladder cancer vaccine, cancer vaccine (Biomira), gastrin 17 immunogen, Maruyama vaccine, melanoma lysate vaccine, melanoma oncolysate vaccine (New York Medical College), melanoma vaccine (New York University), melanoma vaccine (Sloan Kettering Institute), TICE® BCG (Bacillus Calmette-Guerin), and viral melanoma cell lysates vaccine (Royal Newcastle Hospital).

[0204] Non-limiting examples of monoclonal antibodies include abagovomab, adecatumumab, aflibercept, alemtuzumab, blinatumomab, brentuximab vedotin, CA 125 MAb (Biomira), cancer MAb (Japan Pharmaceutical Development), daclizumab, daratumumab, denosumab, edrecolomab, gemtuzumab zogamicin, HER- 2 and Fc MAb (Medarex), ibritumomab tiuxetan, idiotype 105AD7 MAb (CRC Technology), idiotype CEA MAb (Trilex), ipilimumab, lintuzumab, LYM-1 -iodine 131 MAb (Techni clone), mitumomab, moxetumomab, ofatumumab, polymorphic epithelial mucin-yttrium 90 MAb (Antisoma), ranibizumab, rituximab, velutuzumab, and trastuzumab.

[0205] Non-limiting examples of immune checkpoint inhibitors include anti-PD-1 agents or antibodies such as cemiplimab, zimberelimab, nivolumab, and pembrolizumab; anti-PD-L1 agents or antibodies such as atezolizumab, avelumab, and durvalumab; anti-TIGIT agents or antibodies such as tiragolumab and domvanalimab; anti-CTLA-4 agents or antibodies such as ipilimumab and tremelimumab; anti-LAG1 agents; and anti-OX40 agents.

[0206] Non-limiting examples of colony-stimulating factors include darbepoetin alfa, epoetin alfa, epoetin beta, filgrastim, granulocyte macrophage colony stimulating factor, lenograstim, leridistim, mirimostim, molgramostim, nartograstim, pegfilgrastim, and sargramostim.

[0207] Non-limiting examples of additional immunotherapeutic agents include BiTEs, CAR-T cells, GITR agonists, imiquimod, immunomodulatory imides (IMiDs), mismatched double stranded RNA (Ampligen), resiquimod, SRL 172, and thymalfasin.

[0208] Targeted therapy agents include, for example, monoclonal antibodies and small molecule drugs. Non-limiting examples of targeted therapy agents include signal transduction inhibitors, growth factor inhibitors, tyrosine kinase inhibitors, EGFR inhibitors, HER2 inhibitors, histone deacetylase (HDAC) inhibitors, proteasome inhibitors, cell-cycle inhibitors, angiogenesis inhibitors, matrix-metalloproteinase (MMP) inhibitors, hepatocyte growth factor inhibitors, TOR inhibitors, KDR inhibitors, VEGF inhibitors, fibroblast growth factors (FGF) inhibitors, RAF inhibitor, MEK inhibitors, ERK inhibitors, PI3K inhibitors, AKT inhibitors, MCL-1 inhibitors, BCL-2 inhibitors, SHP2 inhibitors, BRAF-inhibitors, RAS inhibitor, heat shock protein (HSP) 90 inhibitor, gene expression modulators, autophagy inhibitors, apoptosis inducers, antiproliferative agents, and glycolysis inhibitors.

[0209] Non-limiting examples of signal transduction inhibitors include tyrosine kinase inhibitors, multiple-kinase inhibitors (i.e., other than Compound (1) or its salt), anlotinib, avapritinib, axitinib,

dasatinib, dovitinib, imatinib, lenvatinib, lonidamine, nilotinib, nintedanib, pazopanib, pegvisomant, ponatinib, vandetanib, and EGFR and/or HER2 inhibitory agents.

[0210] Non-limiting examples of EGFR inhibitors include small molecule antagonists of EGFR such as afatinib, brigatinib, erlotinib, gefitinib, lapatinib, neratinib, dacomitinib, vandetanib, and osimertinib; and antibody-based EGFR inhibitors, including any anti-EGFR antibody or antibody fragment that can partially or completely block EGFR activation by its natural ligand. Antibody-based EGFR inhibitory agents may include, for example, those described in Modjtahedi, H., et al., 1993, Br. J. Cancer 67:247-253; Teramoto, T., et al., 1996, Cancer 77:639-645; Goldstein et al, 1995, Clin. Cancer Res. 1 : 1311-1318; Huang, S. M., et al., 1999, Cancer Res. 15:59(8): 1935-40; and Yang, X., et al., 1999, Cancer Res. 59: 1236-1243; monoclonal antibody Mab E7.6.3 (Yang, 1999 supra); Mab C225 (ATCC Accession No. HB-8508), or an antibody or antibody fragment having the binding specificity thereof; specific antisense nucleotide or siRNA; afatinib, cetuximab; matuzumab; necitumumab; nimotuzumab; panitumumab; and zalutumumab.

[0211] Non-limiting examples of HER2 inhibitors include HER2 tyrosine kinase inhibitors such as afatinib, lapatinib, neratinib, and tucatinib; and anti-HER2 antibodies or drug conjugates thereof such as trastuzumab, trastuzumab emtansine (T-DM1), pertuzumab, margetuximab, trastuzumab deruxtecan (DS-8201a), and trastuzumab duocarmazine. Non-limiting examples of FGFR inhibitors (FGFR-TKI) include anlotinib, ponatinib, dovitinib, lucitanib, lenvatinib, nintedanib, erdafitinib (JNJ-42756493), infigratinib (BGJ398), pemigatinib (INCB054828), rogaratinib (BAY1163877), derazantinib (ARQ 087), futibatinib (TAS-120), LY2874455, AZD4547, Debio 1347, and fisogatinib (BLU-554).

[0212] Non-limiting examples of histone deacetylase (HDAC) inhibitors include belinostat, panobinostat, romidepsin, and vorinostat.

[0213] Non-limiting examples of proteasome inhibitors include bortezomib, carfilzomib, ixazomib, marizomib (salinosporamide a), and oprozomib.

[0214] Non-limiting examples of cell-cycle inhibitors, including CDK inhibitors, include abemaciclib, alvocidib, palbociclib, and ribociclib.

[0215] Non-limiting examples of anti-angiogenic agents (or angiogenesis inhibitors) include, but not limited to, matrix-metalloproteinase (MMP) inhibitors; VEGF inhibitors; EGFR inhibitors; TOR inhibitors such as everolimus and temsirolimus; PDGFR kinase inhibitory agents such as crenolanib; HIF-1 α inhibitors such as PX 478; HIF-2 α inhibitors such as belzutifan and the HIF-2 α inhibitors described in WO 2015/035223; fibroblast growth factor (FGF) or FGFR inhibitory agents such as B-FGF and RG 13577; hepatocyte growth factor inhibitors; KDR inhibitors; anti-Ang1 and anti-Ang2 agents; anti-Tie2 kinase inhibitory agents; Tek antagonists (US 2003/0162712; US 6,413,932); anti-TWEAK agents (US 6,727,225); ADAM disintegrin domain to antagonize the binding of integrin to its ligands (US 2002/0042368); anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (US 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; and 6,057,124); and anti-PDGF-BB antagonists as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands.

[0216] Non-limiting examples of matrix-metalloproteinase (MMP) inhibitors include MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, prinomastat, RO 32-3555, and RS 13-0830. Examples of useful matrix metalloproteinase inhibitors are described, for example, in WO 96/33172, WO 96/27583, EP 1004578, WO 98/07697, WO 98/03516, WO 98/34918, WO 98/34915, WO 98/33768, WO 98/30566, EP 0606046, EP 0931788, WO 90/05719, WO 99/52910, WO 99/52889, WO 99/29667, WO 1999/007675, EP 1786785, EP 1181017, US 2009/0012085, US 5,863,949, US 5,861,510, and EP 0780386. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e., MAP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

[0217] Non-limiting examples of VEGF and VEGFR inhibitory agents include bevacizumab, cediranib, CEP 7055, CP 547632, KRN 633, orantinib, pazopanib, pegaptanib, pegaptanib octasodium, semaxanib, sorafenib, sunitinib, VEGF antagonist (Borean, Denmark), and VEGF-TRAP™.

[0218] Other anti-angiogenic agents may include, but are not limited to, 2-methoxyestradiol, AE 941, alemtuzumab, alpha-D148 Mab (Amgen, US), alphastatin, anecortave acetate, angiocidin, angiogenesis inhibitors, (SUGEN, US), angiostatin, anti-Vn Mab (Crucell, Netherlands), atiprimod, axitinib, AZD 9935, BAY RES 2690 (Bayer, Germany), BC 1 (Genoa Institute of Cancer Research, Italy), beloranib, benefin (Lane Labs, US), cabozantinib, CDP 791 (Celltech Group, UK), chondroitinase AC, cilengitide, combretastatin A4 prodrug, CP 564959 (OSI, US), CV247, CYC 381 (Harvard University, US), E 7820, EHT 0101, endostatin, enzastaurin hydrochloride, ER-68203-00 (IVAX, US), fibrinogen-E fragment, Flk-1 (ImClone Systems, US), forms of FLT 1 (VEGFR 1), FR-111142, GCS-100, GW 2286 (GlaxoSmithKline, UK), IL-8, ilomastat, IM-862, irsogladine, KM-2550 (Kyowa Hakko, Japan), lenalidomide, lenvatinib, MAb alpha5beta3 integrin, second generation (Applied Molecular Evolution, USA and MedImmune, US), MAb VEGF (Xenova, UK), marimastat, maspin (Sosei, Japan), metastatin, motuporamine C, M-PGA, ombrabulin, OXI4503, PI 88, platelet factor 4, PPI 2458, ramucirumab, rBPI 21 and BPI-derived antiangiogenic (XOMA, US), regorafenib, SC-236, SD-7784 (Pfizer, US), SDX 103 (University of California at San Diego, US), SG 292 (Telios, US), SU-0879 (Pfizer, US), TAN-1120, TBC-1635, tesevatinib, tetrathiomolybdate, thalidomide, thrombospondin 1 inhibitor, Tie-2 ligands (Regeneron, US), tissue factor pathway inhibitors (EntreMed, US), tumor necrosis factor-alpha inhibitors, tumstatin, TZ 93, urokinase plasminogen activator inhibitors, vadimezan, vandetanib, vasostatin, vatalanib, VE-cadherin-2 antagonists, xanthorrhizol, XL 784 (Exelixis, US), ziv-aflibercept, and ZD 6126.

[0219] The anticancer agent(s) that may be combined with Compound (1) may also be an active agent that disrupts or inhibits RAS-RAF-ERK or PI3K-AKT-TOR signaling pathways or is a PD-1 and/or PD-L1 antagonist. Examples of which include, but are not limited to, a RAF inhibitor, an EGFR inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a AKT inhibitor, a TOR inhibitor, an MCL-1 inhibitor, a BCL-2 inhibitor, a SHP2 inhibitor, a proteasome inhibitor, or an immune therapy, including

monoclonal antibodies, immunomodulatory imides (IMiDs), anti-PD-1, anti-PDL-1, anti-CTLA4, anti-LAG1, and anti-OX40 agents, GITR agonists, CAR-T cells, and BiTEs.

[0220] Non-limiting examples of RAF inhibitors include dabrafenib, encorafenib, regorafenib, sorafenib, and vemurafenib.

[0221] Non-limiting examples of MEK inhibitors include binimetinib, CI-1040, cobimetinib, PD318088, PD325901, PD334581, PD98059, refametinib, selumetinib, and trametinib.

[0222] Non-limiting examples of ERK inhibitors include LY3214996, LTT462, MK-8353, SCH772984, ravoxertinib, ulixertinib, and ASTX029.

[0223] Non-limiting examples of PI3K inhibitors include 17-hydroxywortmannin analogs (e.g., WO 06/044453); AEZS-136; alpelisib; AS-252424; buparlisib; CAL263; copanlisib; CUDC-907; dactolisib (WO 06/122806); demethoxyviridin; duvelisib; GNE-477; GSK1059615; IC87114; idelalisib; INK1117; LY294002; Palomid 529; paxalisib; perifosine; PI-103; PI-103 hydrochloride; pictilisib (e.g., WO 09/036,082; WO 09/055,730); PIK 90; PWT33597; SF1126; sonolisib; TGI 00-115; TGX-221; XL147; XL-765; wortmannin; taselisib (GDC-0032); and ZSTK474.

[0224] Non-limiting examples of AKT inhibitors include Akt-1-1 (inhibits Akt1) (Barnett et al., (2005) Biochem. J., 385 (Pt. 2), 399-408); Akt-1-1,2 (Barnett et al., (2005) Biochem. J. 385 (Pt. 2), 399-408); API-59CJ-Ome (e.g., Jin et al., (2004) Br. J. Cancer 91, 1808-12); 1-H-imidazo[4,5-c]pyridinyl compounds (e.g., WO05011700); indole-3-carbinol and derivatives thereof (e.g., U.S. Patent No. 6,656,963; Sarkar and Li (2004) J Nutr. 134(12 Suppl), 3493S-3498S); perifosine, Dasmahapatra et al., (2004) Clin. Cancer Res. 10(15), 5242-52, 2004); phosphatidylinositol ether lipid analogues (e.g., Gills and Dennis (2004) Expert. Opin. Investig. Drugs 13, 787-97); triciribine (Yang et al., (2004) Cancer Res. 64, 4394-9); imidazooxazone compounds including trans-3-amino-1-methyl-3-[4-(3-phenyl-5H-imidazo[1,2-c]pyrido[3,4-e][1,3]oxazin-2-yl)phenyl]-cyclobutanol hydrochloride (WO 2012/137870); afuresertib;; capivasertib; 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-1,2,4-triazolo[3,4-f][1,6]naphthyridin-3(2H)-one (MK2206) and pharmaceutically acceptable salts thereof; AZD5363; trans-3-amino-1-methyl-3-(4-(3-phenyl-5H-imidazo[1,2-c]pyrido[3,4-e][1,3]oxazin-2-yl)phenyl)cyclobutanol (TAS-117) and pharmaceutically acceptable salts thereof; and patasertib.

[0225] Non-limiting examples of TOR inhibitors include deforolimus; ATP-competitive TORC1/TORC2 inhibitors, including PI-103, PP242, PP30, and Torin 1; TOR inhibitors in FKBP12 enhancer, rapamycins and derivatives thereof, including temsirolimus, everolimus, WO 9409010; rapalogs, e.g. as disclosed in WO 98/02441 and WO 01/14387, e.g. AP23573, AP23464, or AP23841; 40-(2-hydroxyethyl)rapamycin, 40-[3-hydroxy(hydroxymethyl)methylpropanoate]-rapamycin; 40-epi-(tetrazolyl)-rapamycin (also called ABT578); AZD8055; 32-deoxorapamycin; 16-pentynyloxy-32(S)-dihydrorapamycin, and other derivatives disclosed in WO 05/005434; derivatives disclosed in US 5,258,389, WO 94/090101, WO 92/05179, US 5,118,677, US 5,118,678, US 5,100,883, US 5,151,413, US 5,120,842, WO 93/111130, WO 94/02136, WO 94/02485, WO 95/14023, WO 94/02136, WO 95/16691, WO 96/41807, WO 96/41807 and US 5,256,790; and phosphorus-containing rapamycin derivatives (e.g., WO 05/016252).

[0226] Non-limiting examples of MCL-1 inhibitors include AMG-176, MIK665, and S63845.

[0227] Non-limiting examples of SHP2 inhibitors include JAB-3068, RMC-4630, TNO155, SHP-099, RMC-4550, and SHP2 inhibitors described in WO 2019/167000, WO 2020/022323 and WO2021/033153.

[0228] Non-limiting examples of RAS inhibitors include AMG510 (sotorasib), MRTX849 (adagrasib), LY3499446, JNJ-74699157 (ARS-3248), ARS-1620, ARS-853, GDC-6036, D-1553, JDQ433, JAB-21822, RM-007, RM-008, MRTX1133, and KRpep-2d. Non-limiting examples of HSP90 inhibitors include pimitespi.

[0229] Additional non-limiting examples of anticancer agents that may be suitable for use include, but are not limited to, 2-ethylhydrazide, 2,2',2''-trichlorotriethylamine, ABVD, aceglatone, acemannan, aldophosphamide glycoside, alpharadin, amifostine, aminolevulinic acid, anagrelide, ANCER, ancestim, anti-CD22 immunotoxins, antitumorigenic herbs, apaziquone, arglabin, arsenic trioxide, azathioprine, BAM 002 (Novelos), bcl-2 (Genta), bestabucil, biricodar, bisantrene, bromocriptine, brostallicin, bryostatins, buthionine sulfoximine, calyculin, cell-cycle nonspecific antineoplastic agents, celmoleukin, clodronate, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), defofamine, denileukin diftitox, dexrazoxane, diaziquone, dichloroacetic acid, dilazep, discodermolide, docosanol, doxercalciferol, edelfosine, eflornithine, EL532 (Elan), elfomithine, elsamitucin, eniluracil, etanidazole, exisulind, ferruginol, folic acid replenisher such as frolic acid, gacytosine, gallium nitrate, gimeracil/oteracil/tegafur combination (S-1), glycopine, histamine dihydrochloride, HIT diclofenac, HLA-B7 gene therapy (Vical), human fetal alpha fetoprotein, ibandronate, ibandronic acid, ICE chemotherapy regimen, imexon, iobenguane, IT-101 (CRLX101), laniquidar, LC 9018 (Yakult), leflunomide, lentinan, levamisole + fluorouracil, lovastatin, lucanthone, masoprocol, melarsoprol, metoclopramide, miltefosine, miproxifene, mitoguazone, mitozolomide, mopidamol, motexafin gadolinium, MX6 (Galderma), naloxone + pentazocine, nitracrine, nolatrexed, NSC 631570 octreotide (Ukraine), olaparib, P-30 protein, PAC-1, palifermin, pamidronate, pamidronic acid, pentosan polysulfate sodium, phenamet, picibanil, pixantrone, platinum, podophyllinic acid, porfimer sodium, PSK (Polysaccharide-K), rabbit antithymocyte polyclonal antibody, rasburicombodiment, retinoic acid, rhenium Re 186 etidronate, romurtide, samarium (153 Sm) lexidronam, sizofiran, sodium phenylacetate, sparfosic acid, spirogermanium, strontium-89 chloride, suramin, swainsonine, talaporfin, tariquidar, tazarotene, tegafur-uracil, temoporfin, tenuazonic acid, tetrachlorodecaoxide, thrombopoietin, tin ethyl etiopurpurin, tirapazamine, TLC ELL-12, tositumomab-iodine 131, trifluridine and tipiracil combination, troponin I (Harvard University, US), urethan, valspodar, verteporfin, zoledronic acid, and zosuquidar.

[0230] Additional non-limiting examples of anticancer agents that may be suitable for use include, but are not limited to, futibatinib, zipalertinib, tolinapant, FTD/TPI, TAS2940, TAS3351 and TAS0612.

[0231] In some embodiments, the other therapeutic agents may be selected from the group consisting of: ADI-PEG 20, AMG-176, APG-115, APR-246, avelumab, bendamustine, bisantrene, brentuximab vedotin, capecitabine, CB-839, cisplatin, CS-01, cusatuzumab, cyclophosphamide, cytarabine, dasatinib, daunorubicin, DCLL9718S, decitabine, deferasirox, dexamethasone, durvalumab, eltrombopag,

enasidenib, entinostat, entrectinib, enzalutamide, epacadostat, erythropoietin, etoposide, evorpacept, filgrastim, fludarabine phosphate, flumatinib, gemcitabine, gemtuzumab ozogamicin, gilteritinib, GM-CSF, GSK2879552, HMPL-523, homoharringtonine, IBI188, ibrutinib, idarubicin, itacitinib, ivosidenib, jaktinib, KPT-8602, LDE255, lenalidomide, lirilumab, LP-108, magrolimab, MAX-40279, mitoxantrone, mitoxantrone liposome, mocetinostat, moxifloxacin, nivolumab, olutasidenib, omacetaxine, oxaliplatin, paclitaxel, pembrolizumab, pevonedistat, pinometostat, pracinostat, quizartinib, revlimid, rigosertib, rituximab, romidepsin, RP7214, S64315, S65487, sabatolimab, seclidemstat, selumetinib, siremadlin, sirolimus, SL-401, SNDX-5613, sorafenib, talazoparib, tamibarotene, tolinapant, trastuzumab, tucidinostat, tyrosine kinase inhibitor, uproleselan, velcade, venetoclax, vincristine, visilizumab, vorinostat, and vosaroxin. In the treatment of any of conditions described herein, the pharmaceutical composition or dosage form described herein, may be administered in combination with non-chemotherapeutic treatments, such as iron, all-trans retinoic acid, allogeneic stem cell transplantation and/or platelet transfusions.

Kits

[0232] Provided herein are kits that include a dosage form of the disclosure, and suitable packaging. In one embodiment, a kit further includes a label and/or instructions for use of the dosage form in the treatment of the indications, including the diseases or conditions, described herein.

Dosage Forms & Excipients

[0233] The oral dosage forms described herein are prepared in a manner well known in the pharmaceutical art. *See, e.g.*, Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0234] Some embodiments described herein may be modified to include any additional suitable excipients. Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxybenzoates; sweetening agents; and flavoring agents.

[0235] For preparing solid compositions such as tablets or capsules, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, prodrug, or deuterated analog thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[0236] The tablets or pills of the compounds described herein may be formulated to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope or coat over the former. The two components can be separated by a seal coat layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials include a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0237] In some embodiments, the pellets and/or tablets described herein further comprise a film coating e.g., for limiting photolytic degradation. Suitable film coatings are selected by routine screening of commercially available preparations. In one embodiment, the film coating may be a polyvinylalcohol-based coating.

[0238] In some embodiments, the pharmaceutical compositions as described herein are formulated in a unit dosage or pharmaceutical dosage form. The term “unit dosage forms” or “pharmaceutical dosage forms” refers to physically discrete units suitable as unitary dosages for human patients and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient and are provided, for example, as a capsule. The dosage forms are generally administered in a pharmaceutically effective amount. In some embodiments, the dosage forms are placed/stored in aluminum strip packing, moisture barrier blister foil, or bottle packs.

EMBODIMENTS

[0239] Embodiment 1. A pharmaceutical dosage form comprising: about 20 mg of cedazuridine; and about 100 mg to about 160 mg of azacitidine.

[0240] Embodiment 2. The pharmaceutical dosage form of embodiment 1, wherein cedazuridine is formulated for immediate release.

[0241] Embodiment 3. The pharmaceutical dosage form of embodiment 1 or 2, wherein at least a portion of azacitidine is formulated for enteric release.

[0242] Embodiment 4. The pharmaceutical dosage form of any one of embodiments 1-3, wherein azacitidine is provided as minitablets comprising an enteric coat.

[0243] Embodiment 5. The pharmaceutical dosage form of embodiment 4, wherein the enteric coat comprises polymethacrylate or copolymers thereof.

[0244] Embodiment 6. The pharmaceutical dosage form of embodiment 4 or 5, wherein the enteric coat is sensitive to pH variations in the intestine.

[0245] Embodiment 7. The pharmaceutical dosage form of any one of embodiments 4-6, wherein each azacitidine minitablet comprises: about 20%-60% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets; and one or more pharmaceutically acceptable excipients.

- [0246] Embodiment 8. The pharmaceutical dosage form of embodiment 7, wherein the one or more pharmaceutically acceptable excipients is selected from the group consisting of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose sodium, silicon dioxide, and magnesium stearate.
- [0247] Embodiment 9. The pharmaceutical dosage form of any one of the preceding embodiments, comprising about 130 to 150 mg of azacitidine.
- [0248] Embodiment 10. The pharmaceutical dosage form of any one of embodiments 1-8, comprising about 100 to 120 mg of azacitidine.
- [0249] Embodiment 11. The pharmaceutical dosage form of any one of embodiments 1-8, comprising about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine.
- [0250] Embodiment 12. The pharmaceutical dosage form of any one of the preceding embodiments, wherein the cedazuridine is uncoated and in the form of minitabets, a tablet, powder, blend, granules, or pellets.
- [0251] Embodiment 13. A capsule comprising: one or more azacitidine minitabets formulated for modified release, comprising about 100 mg to about 160 mg of azacitidine, pharmaceutically acceptable excipients, and an enteric coat; and immediate release cedazuridine in a form of uncoated powder or blends, comprising about 20 mg of cedazuridine and pharmaceutically acceptable excipients.
- [0252] Embodiment 14. The capsule of embodiment 13, comprising about 130 to 150 mg of azacitidine.
- [0253] Embodiment 15. The capsule of embodiment 13, comprising about 100 to 120 mg of azacitidine.
- [0254] Embodiment 16. The capsule of embodiment 13, comprising about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine.
- [0255] Embodiment 17. A method of treating cancer in a patient comprising administering the dosage form of any one of embodiments 1 to 12, or the capsule of any one of claims 13-16, to the patient in need thereof.
- [0256] Embodiment 18. The method of embodiment 17, wherein the cancer is leukemia.
- [0257] Embodiment 19. The method of embodiment 17, wherein the cancer is selected from the group consisting of previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.
- [0258] Embodiment 20. The method of embodiment 17, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously

treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) chronic myeloid leukemia (CML).

[0259] Embodiment 21. The method of any one of embodiments 17 to 20, further comprising administering another therapeutic agent.

[0260] Embodiment 22. The method of embodiment 21, wherein the another therapeutic agent is one or more selected from the list consisting of: ADI-PEG 20, AMG-176, APG-115, APR-246, avelumab, bendamustine, bisantrene, brentuximab vedotin, capecitabine, CB-839, cisplatin, CS-01, cusatuzumab, cyclophosphamide, cytarabine, dasatinib, daunorubicin, DCLL9718S, decitabine, deferasirox, dexamethasone, durvalumab, eltrombopag, enasidenib, entinostat, entrectinib, enzalutamide, epacadostat, erythropoietin, etoposide, evorpacept, filgrastim, fludarabine phosphate, flumatinib, gemcitabine, gemtuzumab ozogamicin, gilteritinib, GM-CSF, GSK2879552, HMPL-523, homoharringtonine, IBI188, ibrutinib, idarubicin, itacitinib, ivosidenib, jaktinib, KPT-8602, LDE255, lenalidomide, lirilumab, LP-108, magrolimab, MAX-40279, mitoxantrone, mitoxantrone liposome, mocetinostat, moxifloxacin, nivolumab, olutasidenib, omacetaxine, oxaliplatin, paclitaxel, pembrolizumab, pevonedistat, pinometostat, pracinostat, quizartinib, revlimid, rigosertib, rituximab, romidepsin, RP7214, S64315, S65487, sabatolimab, seclidemstat, selumetinib, siremadlin, sirolimus, SL-401, SNDX-5613, sorafenib, talazoparib, tamibarotene, tolinapant, trastuzumab, tucidinostat, tyrosine kinase inhibitor, uproleselan, velcade, venetoclax, vincristine, visilizumab, vorinostat, and vosaroxin.

[0261] Embodiment 23. A pharmaceutical dosage form according to any one of embodiments 1 to 12, or a capsule according to any one of embodiments 13 to 16, for use in the treatment of cancer.

[0262] Embodiment 24. A pharmaceutical dosage form according to any one of embodiments 1 to 12, or a capsule according to any one of claims 13 to 16, for use in manufacturing a medicament for the treatment of cancer.

[0263] Embodiment 25. The pharmaceutical dosage form or capsule for use according to embodiment 23 or 24, wherein the cancer is leukemia.

[0264] Embodiment 26. The pharmaceutical dosage form or capsule for use according to claim 23 or 24, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.

[0265] Embodiment 27. The pharmaceutical dosage form or capsule for use according to embodiment 23 or 24, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary

chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) chronic myeloid leukemia (CML).

[0266] Embodiment 28. Use of the pharmaceutical dosage form according to any one of embodiments 1 to 12, or a capsule according to any one of claims 13 to 16, for the treatment of cancer.

[0267] Embodiment 29. Use of the pharmaceutical dosage form according to any one of claims 1 to 12, or a capsule according to any one of embodiments 13 to 16, for the manufacture of medicament for the treatment of cancer.

[0268] Embodiment 30. The use of claim 28 or 29, wherein the cancer is leukemia.

[0269] Embodiment 31. The use of embodiment 28 or 29, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.

[0270] Embodiment 32. The use of embodiment 28 or 29, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), and previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML).

EXAMPLES

[0271] The following examples are included to demonstrate specific embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques to function well in the practice of the disclosure, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

Example 1: Uncoated cedazuridine 20 mg tablet & 4 mg azacitidine (intragranular and extragranular layers) minitablets

Manufacturing Process

[0272] 20 mg cedazuridine round tablet was prepared by direct compression. The composition of the cedazuridine core is presented in **Table 1-1**. Individual excipients and cedazuridine, except magnesium stearate, were screened through 30 mesh and blended for 15 minutes at 25 rpm in a 1.5L V-blender. The blended cedazuridine and excipients were then mixed with hand screened magnesium stearate and blended again for 3 minutes at 25 rpm. The final blend was compressed into round (0.25" inch) tablet by

direct compression on a Korsch XL-100 press. Cedazuridine tablet was not coated and used as immediate release minitablets.

Table 1-1: 20 mg Cedazuridine tablet composition

Ingredients	Cedazuridine 20 mg	
	mg/tab	%
Cedazuridine	20.0	20.0
Lactose monohydrate (FlowLac® 90)	71.5	71.5
Croscarmellose Sodium (Ac-Di-Sol® SD-711)	5.0	5.0
Hypromellose E5 2910	2.0	2.0
Colloidal Silicon Dioxide	1.0	1.0
Magnesium Stearate (Hyqual®, Vegetal)	0.5	0.5
Core tablet total, Oval	100 mg	100

[0273] Azacitidine minitablets having intragranular and extragranular layers, having two different composition of **Table 1-2** (“Core 1” and “Core 2”), were prepared. Azacitidine and all intragranular excipients were dispensed into individual containers and screened through 30 mesh. Sieved azacitidine and intragranular excipients except for magnesium stearate were added into a blender with a suitable capacity and mixed at 25 rpm at predetermined duration. Magnesium stearate for intragranular layer was then sieved and added to the blend, and the lubrication blending was performed. The intragranular blend was then roller compacted into ribbons and ribbons were milled into granules. Milled granules were blended with screened extra granular excipients to make final blend. The final blend was compressed into minitablets tablets using 2.5-mm round, plain face tooling. The target weight of the tablets was 10 mg $\pm$ 10% and a target hardness range was between 1- 3 kp.

Table 1-2: 4 mg Azacitidine minitablet core composition

Ingredients	Core 1		Core 2	
	mg/tab	%	mg/tab	%
Intragranular				
Azacitidine	4.0	40.0	4.03	40.0
MCC (PH 102)	2.5	25.0	2.50	25.0
Lactose Monohydrate (Flow Lac 90)	1.99	19.9	1.94	19.4
Croscarmellose Sodium	0.25	2.5	0.25	2.5
Hypromellose E6	-	-	0.20	2.0
Kollidone VA64	0.2	2.0	-	-
Aerosil 200 or CabOsil (Colloidal silicon dioxide)	0.05	0.5	0.05	0.5
Magnesium Stearate	0.08	0.8	0.08	0.8
Extragranular				
Avicel PH200 (Microcrystalline cellulose)	-	-	0.50	5.0
Avicel PH102 (Microcrystalline cellulose)	0.4	4.0		
Croscarmellose sodium	0.25	2.5	0.25	2.5
Colloidal silicon dioxide	0.05	0.5	0.16	1.6
Magnesium stearate	0.02	0.2	0.04	0.4
Kollidon VA64	0.21	2.1	-	-
Core minitablet total, minitablet (2 mm)	10.0 mg	100	10.0 mg	100

[0274] The uncoated tablets were seal coated at 5% weight gain followed by functional coating of Surelease to modulate the dissolution profile. HPMC from Coloron (Opadry® complete coating system YS-1-19025-A-Clear) was used both for seal coat and as a pore former in an ethyl cellulose dispersion (Surelease) for a functional coat. “Core 1” minitablets were coated with 75:25 (Surelease®: Pore Former)

at 20% wt. gain and “Core 2” minitables were coated with 80:20 Surelease: Pore Former coating at 15% wt. gain. Composition of coating is listed in **Tables 1-3** and **1-4**. Both seal coating and functional coating of minitables were performed in a Wuster coater.

Table 1-3: Seal Coat composition (200 mL preparation, 10% solids)

Material	Theoretical amount (g)
Opadry® complete film coating system YS-1-1-19025-A-Clear	20
Water	180

Table 1-4: Surelease composition (500 mL preparation, 10% solids)

Material	Theoretical amount (g) for 75/25 (Surelease : Pore Former)	Theoretical amount (g) for 80/20 (Surelease : Pore Former)
Opadry® complete film coating system YS-1-1-19025-A-Clear	12.5	10.0
Surelease®*	150.0	160.0
Water	337.5	330.0

*Surelease dispersion at 25% solids

Dissolution Profile

[0275] For dissolution testing, five (5) coated or uncoated azacitidine minitables at each weight gain (15% and 20%) were placed in a size 0, VCAPS Plus capsule for a total dose of 20 mg and tested for dissolution. Dissolution testing was carried out in 500 mL, pH 6.8, 50 mM sodium phosphate buffer at 37°C bath temperature with an agitation speed of 75 rpm in a basket. The drug release data was collected at 0, 30, 45, 60, 90, 120, 180 mins and at 195 mins (deemed infinity) with 250 rpm speed. The release profile for all 3 groups is presented in **FIG. 1**.

[0276] As shown in **FIG. 1**, the dissolution results showed uncoated azacitidine minitables released azacitidine within 30 mins followed by 15% coated azacitidine minitables at 80/20 Surelease: Pore former ratio and then 20% coated azacitidine minitables with 75/25 Surelease: pore former ratio. The drug release extended to 90 mins and 120 mins with 15% and 20% coated minitables, respectively.

Example 2: Uncoated Cedazuridine 20mg Tablet & 3 Layer Coated 4mg Azacitidine (intragranular and extragranular layers) Minitables

Manufacturing Method

[0277] The uncoated cedazuridine 20 mg minitables and the uncoated azacitidine 4 mg minitables were prepared using the method described in Example 1. The composition for cedazuridine and azacitidine minitables are shown in Tables 2-1 and 2-2.

Table 2-1: 20 mg Cedazuridine tablet composition

Ingredients	Cedazuridine 20mg	
	mg/tab	%
Cedazuridine	20.0	20.0
Lactose monohydrate (FlowLac® 90)	71.5	71.5
Croscarmellose Sodium (Ac-Di-Sol® SD-711)	5.0	5.0
Hypromellose E5 2910	2.0	2.0
Colloidal Silicon Dioxide	1.0	1.0
Magnesium Stearate (Hyqual®, Vegetal)	0.5	0.5
Core minitablet total, Oval	100 mg	100

Table 2-2: Formulation Composition of 4 mg Azacitidine minitablets

Material	Function	% w/w	Unit dose mg/tablet
Azacitidine	API	40.0	4.0
Lactose monohydrate, Flowlac 90	Diluent	19.9	1.99
Microcrystalline cellulose, PH102	Diluent	25.0	2.5
Croscarmellose sodium, AcDiSol SD-711	Disintegrant	2.5	0.25
Kollidon VA 64	Binder	2.0	0.2
Colloidal silicon dioxide	Glidant	0.5	0.05
Magnesium Stearate, Emprove, Vegetable	Lubricant	0.8	0.08
Total Intragranular		90.7	9.07
Extragranular			
Microcrystalline cellulose, PH200	Diluent	4.0	0.4
Croscarmellose sodium, AcDiSol SD-711	Disintegrant	2.5	0.25
Kollidon VA 64	Binder	2.1	0.21
Colloidal silicon dioxide, Aerosil 200	Glidant	0.5	0.05
Magnesium Stearate, Emprove, Vegetable	Lubricant	0.2	0.02
Total Extragranular		9.3	0.93
Core minitablet total, round		100	10

[0278] The uncoated azacitidine minitablets were seal coated at 2% weight gain followed by intermediate coating at 20% wt. gain, and a final coat of Eudragit® polymer at two polymer weight gains of 5.3% which corresponds to 8.5% total weight gain.

[0279] Both seal coating and functional coating of minitablets were performed in a Wuster coater. The composition of seal, intermediate and functional coatings is presented in Tables 2-3, 2-4 and 2-5 respectively.

Table 2-3: Composition for seal coating for 2% wt. gain

Ingredients	HPMC E3	
	Quantity (g)	%
HPMC E3 (JRS Pharma)	6.0	6.82
PEG 600 (TCI)	0.6	0.68
Purified water	81.4	92.5
Total	88.0	100.0
Solid content	7.5	

Table 2-4: Composition for intermediate coating for 20% wt. gain

Ingredients	HPMC E3	
	Quantity (g)	%
HPMC E3 (JRS Pharma)	30.0	7.1
Magnesium Oxide Light	30.0	7.1
PEG 600 (TCI)	3.0	0.7
Purified water	357.0	85.0
Total	420.0	100.0
Solid content	15.0	

Table 2-5: Composition of enteric Functional Coating

Ingredients	Quantity (g)	%
Eudragit® L30D-55 (Evonik)	75.0 (22.5 g of solid)	12.5 (solid basis)
Triethyl Citrate	2.25	1.25
Talc	11.25	6.25
Purified water	91.5	50.8
Total	180.0	100.0
Solid content	20.0	

Dissolution Testing

[0280] For dissolution testing, five (5) coated azacitidine minitabets at 5.3% polymer weight gain were placed in a size 1, VCAPS plus capsule for a total dose of 20 mg and tested for dissolution.

[0281] Dissolution testing was carried out in two stages, acid stage, pH 1.2, 0.1N HCl and buffer stage, pH 6.8, 50mM phosphate buffer at 37°C bath temperature with an agitation speed of 75 rpm in a basket and 500mL dissolution media. The minitabets coated with Eudragit® polymer prevented the release of azacitidine in the acid stage followed by rapid release in the buffer stage, 6.8 pH after media switch at 120 mins (**FIG. 2**). As shown in **FIG. 2**, azacitidine was not released for the first 2 hours in acidic condition, while azacitidine was mostly released after being moved to pH 6.8, confirming the pH sensitivity of the Eudragit® L30D coating. Further, Eudragit® coated minitabets at 5.3% wt. gain provided enough protection in the acid stage followed by rapid release in the buffer stage at pH 6.8 after media switch at 120 minutes.

**Example 3-1: Uncoated Cedazuridine 20mg Tablet & 2 Layer Coated 4mg Azacitidine
(intragranular and extragranular layers) Minitabets**

[0282] The uncoated cedazuridine 20 mg tablet of Example 4 were provided. Azacitidine and all intragranular excipients except magnesium stearate listed in **Table 3-1** were dispensed into 8 Qt. V Shell equipped on PK blender and mixed for 10 minutes at 25 rpm. The preblend was screened through a Quadro Comil Model U3 equipped with a 032R screen and a round impeller at a speed 4500 +/- 100 rpm. The screened material was transferred back into the blender and mixed again for 10 minutes at 25 rpm. Magnesium stearate was hand screened through 30 mesh and added into a blender and mixed for 10 mins at 25 rpm. The intragranular blend was roller compacted on a Alexanderwerk roller compactor at roller speed of 4.0 rpm, compaction force of 4.0KN/cm and feed screw speed at 20 rpm. The ribbons were milled on a granulator at speed 100 rpm speed equipped with 0.80 mm screen. The extragranular excipient quantity was adjusted based on the yield of intragranular milled granules. Extragranular excipients were hand screened through 30 mesh. Both intragranular milled granules and extragranular excipients except magnesium stearate were transferred into the blender and mixed for 10 minutes at 25 rpm. Screened magnesium stearate was added to the blended material and mixed for 3 minutes at 25 rpm. The final blend was compressed into minitabets using round tooling of 2.5 mm diameter on a Natoli RD30 press. The target weight of the minitabets was 10 mg ± 1.0 mg and hardness 1-3 KP as determined on a Hardness Testor by Scotax.

Table 3-1: Azacitidine 4mg uncoated minitablets

Ingredient	mg	%
Intragranular		
Azacitidine	4.0	40.0
Lactose monohydrate	1.97	19.7
MCC (Avicel® PH-102)	2.50	25.0
Croscarmellose Sodium	0.25	2.5
Hypromellose	0.20	2.0
Colloidal silicon Dioxide	0.05	0.5
Magnesium Stearate	0.08	0.8
Intragranular Total	9.05	90.5
Extragranular		
MCC (Avicel® PH-102)	0.5	5.0
Croscarmellose Sodium	0.25	2.5
Colloidal Silicon Dioxide	0.16	1.6
Magnesium Stearate	0.04	0.4
Extragranular Total	0.95	9.5
Core minitabket total	10.0	100.0

[0283] The uncoated azacitidine 4 mg minitablets were coated using ingredients listed in Tables 3-2 and 3-3, using the method described in Example 2. Weight gains of 15% or 20% were employed.

Table 3-2: Seal coating composition

Ingredient	%
Opadry Clear, YS-1-19025-A (HPMC based)	10
Purified water	90

Table 3-3: Release modulating coat

Ingredient	%
Opadry clear, YS-1-19025-A (HPMC based)	2.0 – 2.5
Surelease® E-7-19040 (Ethyl cellulose based)	7.5 – 8.0
Milli-Q water	90

**Example 3-2: Uncoated Cedazuridine 20mg Tablet & 3 Layer Coated 4mg Azacitidine
(intragranular and extragranular layers) Minitablets**

[0284] Instead of coatings as described in Example 3-1, the uncoated azacitidine 4 mg minitablets comprising intragranular and extragranular layers were seal coated in two layers, using ingredients listed in Tables 3-4 (first layer) and 3-5 (second layer). The seal coated azacitidine pellets were further coated with delayed release coating, using ingredients listed in Table 3-6.

Table 3-4: Seal coat first layer

Ingredient	%
HPMC E5	7.5
Purified water	92.5

Table 3-5: Seal coat second layer

Ingredient	%
HPMC E3	7.5
Magnesium oxide, light	7.5
Purified water	85

Table 3-6: Delayed release coating

Ingredient	%
Eudragit® L30D-55	41.7
Triethyl citrate	1.25
Talc	6.25
Purified water	50.8

**Example 4: Uncoated Cedazuridine 20mg Tablet & 2 Layer Coated 4mg Azacitidine
(Intragranular and Extragranular layers) Minitablets**

Manufacturing Process

[0285] 20 mg cedazuridine round tablets were prepared by direct compression. The composition of cedazuridine core tablets is listed in **Table 4-1**. Individual excipients and cedazuridine except magnesium stearate were screened through 30 mesh and blended in a V-blender, 1.5L for 15-20 minutes. Blended cedazuridine and excipients were then mixed with screened magnesium stearate and blended again in a V-blender for 5 minutes. Cedazuridine tablets were compressed into round (0.25" inch) tablets by direct compression on a Korsch XL-100 press.

Table 4-1: 20 mg Cedazuridine tablet composition

Ingredients	Cedazuridine 20 mg	
	mg/tab	%
Cedazuridine	20.0	20.0
Lactose monohydrate (FlowLac® 90)	71.5	71.5
Croscarmellose Sodium (Ac-Di-Sol® SD-711)	5.0	5.0
Hypromellose E5 2910	2.0	2.0
Colloidal Silicon Dioxide	1.0	1.0
Magnesium Stearate (Hyqual®, Vegetal)	0.5	0.5
Core tablet total, Oval	100 mg	100

[0286] Azacitidine and all intragranular excipients were dispensed into individual containers and screened through 30 mesh. The composition of azacitidine core tablets is listed in **Table 4-2**. Sieved azacitidine and intragranular excipients except for magnesium stearate were added into a 5 L Bohle blender and mixed at 25 rpm for 10 mins. Magnesium stearate was then sieved and added to the blend, and the lubrication blending was performed for 3 mins at 25 rpm in a 5 L Bohle blender. The intragranular blend was roller compacted into ribbons on a Gerateis FMX1064 and ribbons were milled into granules. Milled granules were blended with screened extra granular excipients except magnesium stearate in the same 5L Bohle blender for 10 minutes at 25 rpm. Screened magnesium stearate was added to the rest of the blend and mixed again for 3 minutes at 25 rpm. The final blend was compressed into minitables using 2.5-mm round, plain face tooling. The target weight of the tablets was 10 mg $\pm$ 10% and a target hardness range between 1- 3 kp.

Table 4-2: Azacitidine 4mg uncoated minitablets

Ingredient	mg	%
Intragranular		
Azacitidine	4.0	40.0
Lactose monohydrate (FlowLac 90)	1.97	19.7
MCC (Avicel® PH-102)	2.50	25.0
Croscarmellose Sodium (Ac-di-sol SD-711)	0.25	2.5
Hypromellose E5	0.20	2.0
Colloidal silicon Dioxide	0.05	0.5
Magnesium Stearate (Emprove, Vegetable)	0.08	0.8
Intragranular Total	9.05	90.5
Extragranular		
MCC (Avicel® PH-200)	0.5	5.0
Croscarmellose Sodium (AcDiSol SD-711)	0.25	2.5
Colloidal Silicon Dioxide (Aerosil 200)	0.16	1.6
Magnesium Stearate, Emprove, Vegetable	0.04	0.4
Extragranular Total	0.95	9.5
Core minitabket total	10.0	100.0

[0287] The uncoated minitablets were seal coated at 2% weight gain followed functional coating with Eudragit® polymer (L30D-55) at polymer weight gain 4.0%. Both seal and functional coating of minitablets were performed in a Wurster coater, GPCG2, 3L. The composition of seal coat and enteric coat is presented in Tables 4-3 and 4-4.

Table 4-3: Azacitidine Seal Coat Composition

Ingredient	Supplier	Quantity (g)
HPMC E3	Viva Pharma	12
PEG 600	TCI	12
Purified water		162.8
Total dispersion		176.8

Table 4-4: Azacitidine Functional Coat Composition

Ingredient	Supplier	Quantity (g)
Eudragit® L30 D-55	Evonik	150
Triethyl citrate	Spectrum	4.5
Talc	Spectrum	22.5
Purified water		183
Total dispersion		360

[0288] The final composition of the coated minitablets is presented in Table 4-5.

Table 4-5: 4 mg Azacitidine minitab with coating composition

Ingredient	mg/tab	(%)
Tablet core: Intragranular		
Azacitidine	4.0	36.24
Microcrystalline cellulose (PH-102)	2.50	22.65
Lactose Monohydrate	1.97	17.85
Croscarmellose Sodium	0.25	2.27
Hypromellose 2910	0.20	1.81
Colloidal silicon dioxide	0.05	0.45
Magnesium Stearate	0.08	0.73
Intragranular total	9.05	82.00
Tablet core: Extragranular		
Microcrystalline cellulose (PH-200)	0.50	4.53
Croscarmellose sodium	0.25	2.26
Colloidal silicon dioxide	0.16	1.45
Magnesium stearate	0.04	0.36
Extragranular total	0.95	8.60
Tablet core total	10.00	90.60
Seal coat (applied on minitab)		
Hypromellose	0.20	1.81
Polyethylene glycol 600	0.02	0.18
Seal coat total	0.22	1.99
Enteric coat (applied on minitab)		
Eudragit® L30D 55	0.51	4.63
Triethyl citrate	0.05	0.46
Talc	0.26	2.32
Enteric coat total	0.82	7.41
Total coated minitab	11.04	100.00

Dissolution Testing

[0289] For dissolution testing, five (5) coated azacitidine minitabets at 4.0% polymer weight gain were placed in a size 1, VCAP plus capsule for a total dose of 20 mg and tested for dissolution. Dissolution testing was carried out in two stages, acid stage, pH 1.2, 0.1N HCl and buffer stage, pH 6.8, 50mM phosphate buffer at 37°C bath temperature with an agitation speed of 75 rpm in a basket and 500mL dissolution media. As shown in FIG. 3, the minitabets coated with Eudragit® polymer prevented the release of azacitidine in the acid stage followed by rapid release in the buffer stage, 6.8 pH after media switch at 120 mins.

[0290] To test dissolution of the enteric coated azacitidine minitabets at various pHs, five (5) enteric coated azacitidine minitabets were placed in a size 0, Vcaps® Plus capsule and tested for dissolution. Dissolution testing was carried out in 6 groups in each of pH 2.3, 3.0, 4.5, 5.2, 5.5, and 6.0 buffers, at 37°C bath temperature with an agitation speed of 75 rpm in a basket. The drug release data was collected at 0, 15, 30, 45, 60, 90 and 120 mins (deemed infinity) with 250 rpm speed. The release profile for all 6 groups is presented in FIG. 4. As shown in FIG. 4, azacitidine dissolved well at pH 6.0 and pH 5.5, while did not dissolve at other pHs.

Example 5: Clinical Data using Combination of Example 4

[0291] For this study, azacitidine was delivered as a delayed release at 4.0% enteric coating weight gain, as described in Example 4. Cedazuridine was delivered as an immediate release. Azacitidine was delivered in the form of minitabets in a HPMC capsule for PK study. Each minitabets contained 4 mg of azacitidine as described in Example 6. The inner most layer is a seal coat followed by a final outer enteric coat with an Eudragit® polymer. No intermediate coating was applied on the azacitidine minitabets for this round of PK study. Eudragit® L30-D55 polymer was used to provide an enteric coat on azacitidine minitabets.

[0292] Human subjects (n=6) were administered with azacitidine on different occasions. PK Dosing occasions used in this study were as follows: Occasion 1: 60 mg subcutaneous injection of azacitidine, 75 mg/m²; Occasion 2: 60 mg oral azacitidine (4.0% Eudragit® coated) only, once a day; Occasion 3: 60 mg uncoated cedazuridine, oral + 60 mg azacitidine (4.0% Eudragit® coated), oral, once a day.

[0293] Human subjects (n=6) were dosed with Occasion 2 composition (oral Azacitidine only) on day -3 (prior to day 1) ("C1D-3"); Occasion 1 composition (subcutaneous) on day 1 ("C1D1"); and Occasion 3 composition on days 2-7 ("C1D2"- "C1D7"), once a day. Blood samples were collected pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 9 and 24 hours after dosing. The collected blood samples were evaluated for PK data.

[0294] The azacitidine PK data is shown in **Table 5**. As shown in **Table 5**, co-administration with cedazuridine increased T_{max}, C_{max} and AUC for azacitidine, indicating that immediate release cedazuridine increases bioavailability of delayed release azacitidine. Further, oral administration of azacitidine and cedazuridine showed more stable, prolonged release of azacitidine compared to subcutaneous administration of azacitidine.

Table 5

Treatment Occasion	T_{max} (hr)	C_{max} (ng/mL)	AUC₀₋₂₄ (ng*hr/mL)
Occasion 1 (azacitidine, SQ)	0.6	384	761
Occasion 2 (azacitidine DR, PO alone)	1.0	14	30
Occasion 3 (azacitidine DR, PO with cedazuridine)	2.0	219	726

Example 6: Clinical Data using Combination having 136 mg Azacitidine

[0295] For this study, azacitidine was delivered as a delayed release at 4.0% enteric coating weight gain, in the form of minitabets in a HPMC capsule for PK study. Each minitabets contained 4 mg of azacitidine as described in Example 4. Cedazuridine dose remained constant in all the occasions at 20 mg and delivered as an immediate release. The inner most layer is a seal coat followed by a final outer enteric coat with an Eudragit® polymer. No intermediate coating was applied on the azacitidine minitabets for this round of PK study. Eudragit® L30-D55 polymer was used to provide an enteric coat on azacitidine minitabets.

[0296] Human subjects (n=5) were administered with azacitidine. All five subjects were dosed on different occasions as follows: Occasion 1: 136 mg oral azacitidine (4.0% Eudragit® coated) only, once a

day; Occasion 2: subcutaneous injection of azacitidine, 75 mg/m²; Occasion 3: 20 mg uncoated cedazuridine, oral + 136 mg azacitidine (4.0% Eudragit® coated), oral, once a day.

[0297] Human subjects (n=5) were dosed with Occasion 1 composition (oral Azacitidine only) on day -3 (prior to day 1) (“C1D-3”); Occasion 2 composition (subcutaneous) on day 1 (“C1D1”); and Occasion 3 composition on days 2-7 (“C1D2”-“C1D7”), once a day. Blood samples were collected pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, 9 and 24 hours after dosing for Occasions 1 and 3, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after dosing for Occasions 2. The collected blood samples were evaluated for PK data.

[0298] The azacitidine PK data is shown in **FIG. 5**, and AUC, C_{max}, T_{max} are shown in **Table 6**. Also, AUC compared to subcutaneous azacitidine (Occasion 2) is also shown in Table 6. As shown in **Table 6**, co-administration with cedazuridine increased T_{max}, C_{max} and AUC for azacitidine, indicating that immediate release cedazuridine increases bioavailability of delayed release azacitidine. Further, oral administration of azacitidine and cedazuridine showed more stable, prolonged release of azacitidine compared to subcutaneous administration of azacitidine.

Table 6

Treatment Occasion	AUC ₀₋₂₄ ¹ (ng*hr/mL)	AUC (% SC azacitidine)	C _{max} ¹ (ng/mL)	T _{max} ² (hr)
Occasion 1: oral azacitidine DR only (C1D-3)	97 (28%)	14%	63 (26%)	3 (1.5-3)
Occasion 2: subcutaneous (SC) azacitidine (C1D1)	715 (119%)	N/A	478 (101%)	0.5 (0.25-0.5)
Occasion 3 (azacitidine DR, PO with cedazuridine), (C1D2)	482 (44%)	67%	210 (55%)	2.5 (1.5-3)
Occasion 3 (azacitidine DR, PO with cedazuridine), (C1D7)	686 (39%)	96%	213 (62%)	3.5 (3-7)

¹ Geometric mean (%CV)

² Median (range)

Example 7: Clinical Data using Combination having 136 mg Azacitidine

[0299] For this study, azacitidine was delivered as a delayed release at 4.0% enteric coating weight gain, in the form of minitabets in a HPMC capsule for PK study. Each minitabset contained 4 mg of azacitidine as described in Example 4. Cedazuridine dose remained constant in all the occasions at 20 mg and delivered as an immediate release. The inner most layer is a seal coat followed by a final outer enteric coat with an Eudragit® polymer. No intermediate coating was applied on the azacitidine minitabets for this round of PK study. Eudragit® L30-D55 polymer was used to provide an enteric coat on azacitidine minitabets.

[0300] Human subjects (n=14) were administered with azacitidine. All subjects were dosed on different occasions as follows: Occasion 1: 136 mg oral azacitidine (4.0% Eudragit® coated) only, once a day; Occasion 2: subcutaneous injection of azacitidine, 75 mg/m²; Occasion 3: 20 mg uncoated cedazuridine, oral + 136 mg azacitidine (4.0% Eudragit® coated), oral, once a day.

[0301] Human subjects (n=14) were dosed with Occasion 1 composition (oral Azacitidine only) on day -3 (prior to day 1) ("C1D-3"); Occasion 2 composition (subcutaneous) on day 1 ("C1D1"); and Occasion 3 composition on days 2-7 ("C1D2"- "C1D7"), once a day. Blood samples were collected pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing for Occasions 1, pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 for Occasion 2, pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, and 9 for Occasion 3. The collected blood samples were evaluated for PK data.

[0302] The azacitidine PK data is shown in **FIG. 6**, and AUC, C_{max} , T_{max} are shown in **Table 7**. Also, AUC compared to subcutaneous azacitidine (Occasion 2) is also shown in Table 6. As shown in **Table 7**, co-administration with cedazuridine increased T_{max} , C_{max} and AUC for azacitidine, indicating that immediate release cedazuridine increases bioavailability of delayed release azacitidine. Further, oral administration of azacitidine and cedazuridine showed more stable, prolonged release of azacitidine compared to subcutaneous administration of azacitidine. Also, based on the estimate of 7-day azacitidine AUC, total cycle azacitidine exposure of oral delayed release administration (Occasion 3) was about 100% of 75 mg/m² subcutaneous azacitidine administration (Occasion 2).

Table 7

Treatment Occasion	AUC ₀₋₂₄ ¹ (ng*hr/mL)	7-Day Total AUC (0-24h)
Occasion 1: oral azacitidine DR only (C1D-3)	97 (73%)	N/A
Occasion 2: subcutaneous (SC) azacitidine (C1D1)	516 (85%)	5035
Occasion 3 (azacitidine DR, PO with cedazuridine), (C1D2)	734 (90%)	5038
Occasion 3 (azacitidine DR, PO with cedazuridine), (C1D7)	719 (50%)	

¹ Geometric mean (%CV)

Example 8: Clinical Data using Combination having 144 mg Azacitidine

[0303] For this study, azacitidine was delivered as a delayed release at 4.0% enteric coating weight gain, in the form of minitabets in a HPMC capsule for PK study. Each minitabets contained 4 mg of azacitidine as described in Example 4. Cedazuridine dose remained constant in all the occasions at 20 mg and delivered as an immediate release. The inner most layer is a seal coat followed by a final outer enteric coat with an Eudragit® polymer. No intermediate coating was applied on the azacitidine minitabets for this round of PK study. Eudragit® L30-D55 polymer was used to provide an enteric coat on azacitidine minitabets.

[0304] Human subjects (n=14) were administered with azacitidine. All subjects were dosed on different occasions as follows: Occasion 1: 144 mg oral azacitidine (4.0% Eudragit® coated) only, once a day; Occasion 2: subcutaneous injection of azacitidine, 75 mg/m²; Occasion 3: 20 mg uncoated cedazuridine, oral + 136 mg azacitidine (4.0% Eudragit® coated), oral, once a day.

[0305] Human subjects (n=14) were dosed with Occasion 1 composition (oral Azacitidine only) on day -3 (prior to day 1) ("C1D-3"); Occasion 2 composition (subcutaneous) on day 1 ("C1D1"); and Occasion 3 composition on days 2-7 ("C1D2"- "C1D7"), once a day. Blood samples were collected pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing for Occasions 1, pre-dose, and 0.25, 0.5, 0.75, 1,

1.5, 2, 3, 4, 6, and 8 for Occasion 2, pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 7, and 9 for Occasion 3.

The collected blood samples were evaluated for PK data.

[0306] The azacitidine PK data is shown in **FIG. 7**, and AUC, C_{max} , T_{max} are shown in **Table 8**. Also, AUC compared to subcutaneous azacitidine (Occasion 2) is also shown in Table 6. As shown in **Table 8**, co-administration with cedazuridine increased T_{max} , C_{max} and AUC for azacitidine, indicating that immediate release cedazuridine increases bioavailability of delayed release azacitidine. Further, oral administration of azacitidine and cedazuridine showed more stable, prolonged release of azacitidine compared to subcutaneous administration of azacitidine. Also, based on the estimate of 7-day azacitidine AUC, total cycle azacitidine exposure of oral delayed release administration (Occasion 3) was about 111% of 75 mg/m² subcutaneous azacitidine administration (Occasion 2).

Table 8

Treatment Occasion	AUC ₀₋₂₄ ¹ (ng*hr/mL)	7-Day Total AUC (0-24h)
Occasion 1: oral azacitidine DR only (C1D-3)	149 (43%)	N/A
Occasion 2: subcutaneous (SC) azacitidine (C1D1)	601 (47%)	5726
Occasion 3 (azacitidine DR, PO with cedazuridine), (C1D2)	955 (30%)	6331
Occasion 3 (azacitidine DR, PO with cedazuridine), (C1D7)	818 (24%)	

¹ Geometric mean (%CV)

Example 9: Clinical Data using Combination having 140 mg, 144 mg Azacitidine

[0307] The PK study similar to **Example 6** is conducted, except for 140 mg and 144 mg of azacitidine was used in the study, instead of 136 mg of azacitidine as in Example 6. It is contemplated that bioavailability of delayed release azacitidine would be similar to or greater than Example 6, as greater amount of azacitidine was administered.

Example 10: Phase 1 Trial using Combination

[0308] This open-label Phase 1 trial enrolled adult patients with confirmed myelodysplastic syndromes (MDS) and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) overlap syndromes who may benefit from azacitidine. Both immediate (IR) and delayed release (DR) azacitidine formulations at several dose combinations were explored. There were six or more patients per dose cohort.

[0309] Overall, 88 patients received a median of 6.0 treatment cycles. Median age was 72 years old (range 26–87), 35% (n=31) were female, prior treatments included DNMTis (9% [n=8]), luspatercept (3% [n=3]), lenalidomide (3% [n=3]), and erythropoiesis-stimulating agents (3% [n=2]). Of the enrolled patients, 72% (n=63) had MDS, 22% (n=19) had CMML, and 7% (n=6) had non-CMML MDS/MPN overlap. In the dose-escalation part, sensitivity of azacitidine to cytidine deaminase (CDA) inhibition was confirmed with the immediate release formulation. To optimize the dose, six dose combinations of delayed release azacitidine minitablets of Example 4 (60–144 mg) and cedazuridine (20–100 mg) were evaluated. Two doses (136/20 mg and 144/20 mg azacitidine/cedazuridine) were investigated in the dose-expansion part.

[0310] Adverse events (AEs) were reported in 100% (n=88) of pts; 84% (n=74) of pts experienced a Grade ≥ 3 AE; 5% (n=4) of pts discontinued treatment due to an AE. The most common Grade ≥ 3 AEs (any cause) were related to myelosuppression: leukopenia, 27%; neutropenia, 26%; thrombocytopenia, 23%. Gastrointestinal toxicities were similar for the combination of azacitidine(4.0% Eudragit® coated) and cedazuridine, and subcutaneous azacitidine. One patient receiving 136/20 mg azacitidine/cedazuridine had a dose-limiting toxicity (DLT) of prolonged Grade 4 neutropenia possibly related to study drug; no other DLTs were observed. Safety and tolerability up to 144 mg azacitidine (4.0% Eudragit® coated) was confirmed.

[0311] Pharmacokinetic data indicated that 20 mg cedazuridine resulted in sufficient inhibition of cytidine deaminase (CDA) to increase absolute bioavailability of oral azacitidine to about 100% compared to subcutaneous azacitidine administration. In the dose-expansion part, 144/20 mg azacitidine/cedazuridine slightly exceeded the 90–110% range of oral/subcutaneous ratio based on calculated total cycle AUC exposures and 136/20 mg azacitidine/cedazuridine achieved PK AUC in the lower end of the 90–110% range. Accordingly, it is contemplated that 136/20 mg azacitidine/cedazuridine will achieve PK AUC of about 100 % bioavailability compared to subcutaneous azacitidine administration.

[0312] *LINE-1* demethylation data were comparable to those reported for subcutaneous azacitidine. Preliminary clinical efficacy assessments for patients with sufficient follow-up (36.2 mo.; n=33) from immediate release azacitidine cohorts with comparable AUC exposures vs subcutaneous azacitidine had overall survival of 29.5 mo., with complete response (CR) rate, 24%; marrow CR, 24%; stable disease, 33%; and efficacy status unknown, 18%.

* * *

[0313] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0314] The inventions illustratively described herein may suitably be practiced in the absence of any element or elements, limitation, or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising”, “including”, “containing”, etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

[0315] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

[0316] It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages, and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

CLAIMS:

1. A pharmaceutical dosage form comprising:
about 20 mg of cedazuridine; and
about 100 mg to about 160 mg of azacitidine.
2. The pharmaceutical dosage form of claim 1, wherein cedazuridine is formulated for immediate release.
3. The pharmaceutical dosage form of claim 1 or 2, wherein at least a portion of azacitidine is formulated for enteric release.
4. The pharmaceutical dosage form of any one of claims 1-3, wherein azacitidine is provided as minitablets comprising an enteric coat.
5. The pharmaceutical dosage form of claim 4, wherein the enteric coat comprises polymethacrylate or copolymers thereof.
6. The pharmaceutical dosage form of claim 4 or 5, wherein the enteric coat is sensitive to pH variations in the intestine.
7. The pharmaceutical dosage form of any one of claims 4-6, wherein each azacitidine minitablet comprises:
about 20%-60% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets; and
one or more pharmaceutically acceptable excipients.
8. The pharmaceutical dosage form of claim 7, wherein the one or more pharmaceutically acceptable excipients is selected from the group consisting of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose sodium, silicon dioxide, and magnesium stearate.
9. The pharmaceutical dosage form of any one of the preceding claims, comprising about 130 to 150 mg of azacitidine.
10. The pharmaceutical dosage form of any one of claims 1-8, comprising about 100 to 120 mg of azacitidine.
11. The pharmaceutical dosage form of any one of claims 1-8, comprising about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine.
12. The pharmaceutical dosage form of any one of the preceding claims, wherein the cedazuridine is uncoated and in the form of minitablets, a tablet, powder, blend, granules, or pellets.
13. A capsule comprising:

one or more azacitidine minitablets formulated for modified release, comprising about 100 mg to about 160 mg of azacitidine, pharmaceutically acceptable excipients, and an enteric coat; and

immediate release cedazuridine in a form of uncoated powder or blends, comprising about 20 mg of cedazuridine and pharmaceutically acceptable excipients.

14. The capsule of claim 13, comprising about 130 to 150 mg of azacitidine.
15. The capsule of claim 13, comprising about 100 to 120 mg of azacitidine.
16. The capsule of claim 13, comprising about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine.
17. A method of treating cancer in a patient comprising administering the dosage form of any one of claims 1 to 12, or the capsule of any one of claims 13-16, to the patient in need thereof.
18. The method of claim 17, wherein the cancer is leukemia.
19. The method of claim 17, wherein the cancer is selected from the group consisting of previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.
20. The method of claim 17, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) chronic myeloid leukemia (CML).
21. The method of any one of claims 17 to 20, further comprising administering another therapeutic agent.
22. The method of claim 21, wherein the another therapeutic agent is one or more selected from the list consisting of: ADI-PEG 20, AMG-176, APG-115, APR-246, avelumab, bendamustine, bisantrene, brentuximab vedotin, capecitabine, CB-839, cisplatin, CS-01, cusatuzumab, cyclophosphamide, cytarabine, dasatinib, daunorubicin, DCLL9718S, decitabine, deferasirox, dexamethasone, durvalumab, eltrombopag, enasidenib, entinostat, entrectinib, enzalutamide, epacadostat, erythropoietin, etoposide, evorpacept, filgrastim, fludarabine phosphate, flumatinib, gemcitabine, gemtuzumab ozogamicin, gilteritinib, GM-CSF, GSK2879552, HMPL-523, homoharringtonine, IBI188, ibrutinib, idarubicin, itacitinib, ivosidenib, jaktinib, KPT-8602, LDE255, lenalidomide, lirilumab, LP-108, magrolimab, MAX-

40279, mitoxantrone, mitoxantrone liposome, mocetinostat, moxifloxacin, nivolumab, olutasidenib, omacetaxine, oxaliplatin, paclitaxel, pembrolizumab, pevonedistat, pinometostat, pracinostat, quizartinib, revlimid, rigosertib, rituximab, romidepsin, RP7214, S64315, S65487, sabatolimab, seclidmestat, selumetinib, siremadlin, sirolimus, SL-401, SNDX-5613, sorafenib, talazoparib, tamibarotene, tolinapant, trastuzumab, tucidinostat, tyrosine kinase inhibitor, uproleselan, velcade, venetoclax, vincristine, visilizumab, vorinostat, and vosaroxin.

23. A pharmaceutical dosage form according to any one of claims 1 to 12, or a capsule according to any one of claims 13 to 16, for use in the treatment of cancer.
24. A pharmaceutical dosage form according to any one of claims 1 to 12, or a capsule according to any one of claims 13 to 16, for use in manufacturing a medicament for the treatment of cancer.
25. The pharmaceutical dosage form or capsule for use according to claim 23 or 24, wherein the cancer is leukemia.
26. The pharmaceutical dosage form or capsule for use according to claim 23 or 24, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.
27. The pharmaceutical dosage form or capsule for use according to claim 23 or 24, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML).
28. Use of the pharmaceutical dosage form according to any one of claims 1 to 12, or a capsule according to any one of claims 13 to 16, for the treatment of cancer.
29. Use of the pharmaceutical dosage form according to any one of claims 1 to 12, or a capsule according to any one of claims 13 to 16, for the manufacture of medicament for the treatment of cancer.
30. The use of claim 28 or 29, wherein the cancer is leukemia.
31. The use of claim 28 or 29, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-

cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.

32. The use of claim 28 or 29, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), and previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML).

33. A method of treating cancer in a patient comprising administering about 20 mg of cedazuridine; and about 100 mg to about 160 mg of azacitidine.

34. The method of claim 33, wherein cedazuridine and azacitidine are administered together.

35. The method of claim 33 or 34, wherein cedazuridine and azacitidine are formulated into a fixed dose combination.

36. The method of claim 33, wherein cedazuridine and azacitidine are administered separately.

37. The method of any one of claims 33-36, wherein cedazuridine is formulated for immediate release.

38. The method of any one of claims 33-37, wherein at least a portion of azacitidine is formulated for enteric release.

39. The method of any one of claims 33-38, wherein azacitidine is provided as minitablets comprising an enteric coat.

40. The method of claim 39, wherein the enteric coat comprises polymethacrylate or copolymers thereof.

41. The method of claim 39 or 40, wherein the enteric coat is sensitive to pH variations in the intestine.

42. The method of any one of claims 33-41, wherein the cancer is leukemia.

43. The method of any one of claims 33-42, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), malignant peripheral nerve sheath tumors (MPNST), neurological cancer, breast cancer, hormone receptor positive tumor, head and neck cancer, primary central chondrosarcoma, myeloproliferative neoplasm (MPN), recurrent B-cell non-Hodgkin lymphoma, recurrent diffuse large B-cell lymphoma, recurrent Hodgkin lymphoma, relapsed/refractory multiple myeloma (RRMM), metastatic colorectal cancer (mCRC), metastatic castration-resistant prostate cancer (mCRPC), and lung cancer.

44. The method of any one of claims 33-43, wherein the cancer is selected from previously treated or untreated, de novo or secondary myelodysplastic syndromes (MDS), previously treated or untreated, de

novo or secondary chronic myelomonocytic leukemia (CMML), acute myeloid leukemia (AML) chronic myeloid leukemia (CML).

45. A fixed dose combination comprising:
 - about 20 mg of cedazuridine; and
 - about 100 mg to about 160 mg of azacitidine.
46. The fixed dose combination of claim 45, wherein cedazuridine is formulated for immediate release.
47. The fixed dose combination of claim 45 or 46, wherein at least a portion of azacitidine is formulated for enteric release.
48. The fixed dose combination of any one of claims 45-47, wherein azacitidine is provided as minitablets comprising an enteric coat.
49. The fixed dose combination of claim 48, wherein the enteric coat comprises polymethacrylate or copolymers thereof.
50. The fixed dose combination of claim 48 or 49, wherein the enteric coat is sensitive to pH variations in the intestine.
51. The fixed dose combination of any one of claims 48-50, wherein each azacitidine minitablet comprises:
 - about 20%-60% w/w of azacitidine, wherein the percentage by weight is relative to the total weight of the uncoated azacitidine minitablets; and
 - one or more pharmaceutically acceptable excipients.
52. The fixed dose combination of claim 51, wherein the one or more pharmaceutically acceptable excipients is selected from the group consisting of lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose sodium, silicon dioxide, and magnesium stearate.
53. The fixed dose combination of claims 45-52, comprising about 130 to 150 mg of azacitidine.
54. The fixed dose combination of any one of claims 45-52, comprising about 120, 124, 128, 132, 136, 140, 144, 148, 152, or 160 mg of azacitidine.
55. The fixed dose combination of any one of claims 45-54, wherein the cedazuridine is uncoated and in the form of minitablets, a tablet, powder, blend, granules, or pellets.