COMPOSITIONS AND METHODS FOR TREATMENT OF ABNORMAL CELL GROWTH

Claim of Priority

This application claims priority to U.S. provisional application 61/925,467, filed on January 9, 2014 and herein referenced in its entirety.

Field of Invention

This invention relates to compositions, for example oral dosage forms, and methods that are useful in the treatment of abnormal cell growth, such as cancer, in mammals, especially humans.

Background of Invention

Convincing evidence suggests that focal adhesion kinase (FAK), a cytoplasmic, non-receptor tyrosine kinase, plays an essential role in cell-matrix signal transduction pathways (Clark and Brugge 1995, *Science* 268: 233-239) and its aberrant activation is associated with an increase in the metastatic potential of tumors (Owens et al. 1995, *Cancer Research* 55: 2752-2755). FAK was originally identified as a 125 kDa protein highly tyrosine-phosphorylated in cells transformed by v-Src. FAK was subsequently found to be a tyrosine kinase that localizes to focal adhesions, which are contact points between cultured cells and their underlying substratum and sites of intense tyrosine phosphorylation. FAK is phosphorylated and, thus, activated in response to extracellular matrix (ECM)-binding to integrins. Recently, studies have demonstrated that an increase in FAK mRNA levels accompanied invasive transformation of tumors and attenuation of the expression of FAK (through the use of antisense oligonucleotides) induces apoptosis in tumor cells (Xu et al. 1996, *Cell Growth and Diff.* 7: 413-418). In addition to being expressed in most tissue types, FAK is found at elevated levels in most human cancers, for example in highly invasive metastases.

Accordingly, a need exists for compounds (*e.g.*, inhibitors), compositions (e.g, formulations, *e.g.*, oral formulations (*e.g.*, oral dosage forms)), and methods of use of inhibitors of the non-receptor tyrosine kinase, FAK, for use in the treatment of abnormal cell growth. U.S. Pat. No. 8,247,411 relates to a broad class of novel pyrimidine derivatives that are kinase inhibitors, and more specifically, inhibitors of FAK. Compounds such as these may be useful in the treatment of abnormal cell growth.

Summary of the Invention

In one aspect, the present invention comprises a composition, *e.g.*, pharmaceutical composition comprising VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-

6063 hydrochloride), *e.g.*, admixed with an excipient (*e.g.*, a binder, *e.g.*, a polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF); a *e.g.*, polyol (*e.g.*, mannitol-starch (*e.g.*, Pearlitol Flash), mannitol, sorbitol)). In some embodiments, the excipient is a binder. In some embodiments, the excipient is a polymer. In some embodiments, the polymer is a precipitation inhibitor. In some embodiments, the precipitation inhibitor is a HPMCAS. In some embodiments, the precipitation inhibitor is HPMCAS-HF. In some embodiments, the excipient reduces precipitation (*e.g.*, of VS-6063 in solution, *e.g.*, in vivo) when administered orally. In some embodiments, the excipient enhances bioavailability (*e.g.*, improves absorption) of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), when administered orally. In some embodiments, the ratio (*e.g.*, relative amount) by weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), to the polymer is about 1 to 1, 1 to 2, 1 to 3, 1 to 4, 1 to 5, 1 to 6, 1 to 7, 1 to 8, or 1 to 9. In some embodiments, the polymer is a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF). In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present in the composition in an amount that is about 10, 25, 30, 31, 32, 32.5, 33, 34, 35, 40, 45, 50% or more weight per weight (w/w) relative to an amount of polymer, *e.g.*, a precipitation inhibitor, provided. In some embodiments, the composition is admixed with 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15%, or 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the composition. In some embodiments, the polymer is present at 25 to 55%, 35 to 45%, 38 to 43%, or 40% weight of polymer per weight of the oral dosage form. In some embodiments, the polymer is a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF). In some embodiments, the precipitation inhibitor is a HPMCAS. In some embodiments, the precipitation inhibitor is HPMCAS-HF.

In some embodiments, the composition is configured in an oral dosage form. In some embodiments, the oral dosage form comprises 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15%, or 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form. In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 13% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form.

In some embodiments, the oral dosage form is a tablet. In some embodiments, the tablet is provided by direct compression of a physical blend or mixture. In some embodiments, the physical blend or mixture is provided by a dry granulation process.

In some embodiments, the tablet has a tablet hardness of about 5 to 20 kP, 7 to 17 kP, 5 to 15 kP, or 10 to 15 kP. In some embodiments, the tablet has a tablet hardness of about 5, 6, 7, 8, 9, 10, 11, 12, 13 or more kP. In some embodiments, the tablet has a disintegration time of about 1 to 20 mins, 3 to 17 mins, 5 to 15 mins, or 9 to 15 mins. In some embodiments, the tablet has a disintegration time of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more minutes.

In some embodiments, the pharmaceutical composition further comprises one or more fillers (*e.g.*, microcrystalline cellulose (*e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH 102); lactose (*e.g.*, lactose monohydrate (*e.g.*, FastFlo 316)). In some embodiments, the filler is present at 5 to 80%, 10 to 70%, 20 to 60%, 30 to 60%, 30 to 50%, or 42% weight of filler per weight of the oral dosage form. In some embodiments, the filler is a mixture of two fillers. In some embodiments, one filler is a microcrystalline cellulose, microcrystalline cellulose PH 102 (*e.g.*, Avicel PH 102). In some embodiments, one filler is lactose monohydrate (*e.g.*, FastFlo 316). In some embodiments, the filler is present at 10 to 30%, 15 to 25%, or 20% weight of filler per weight of the oral dosage form. In some embodiments, the fillers are present at a 1:1 w/w ratio to one another.

In some embodiments, the oral dosage form comprises a disintegrant (*e.g.*, a polymer, *e.g.*, a crosslinked polymer, *e.g.*, crosslinked polyvinylpyrrolidone or crospovidone, carboxymethyl cellulose or croscarmellose sodium; starch, *e.g.*, modified starch, *e.g.*, sodium starch glycolate). In some embodiments, the disintegrant is sodium starch glycolate. In some embodiments, the disintegrant is present at 0 to 5%, 1 to 5%, 2.5 to 5%, or 3% weight of disintegrant per weight of the oral dosage form.

In some embodiments, the oral dosage form comprises a lubricant (*e.g.*, talc, silica, fats, *e.g.*, magnesium stearate). In some embodiments, the lubricant is magnesium stearate. In some embodiments, the lubricant is present at 0.1 to 2% or 0.2 to 1.5% weight of lubricant per weight of the oral dosage form. In some embodiments, the lubricant is present at 1% w/w. In some embodiments, the lubricant is present at 0.5% w/w.

In an embodiment, an oral dosage form described herein has a greater C_{max} value than a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an admixture. In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.1 times (*e.g.*, at least 1.25 times, at least 1.5 times, at least 2 times, at least 3

times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one aspect, the present invention comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 5 to 50% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, a polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an amount from about 25 to 55% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, microcrystalline cellulose, *e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH102) in an amount from about 10 to 30% by weight on a dry weight basis, a second pharmaceutically acceptable filler (*e.g.*, lactose, *e.g.*, lactose monohydrate, *e.g.*, FastFlo 316) in an amount from about 10 to 30% by weight on a

dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g*, sodium starch glycolate) in an amount from about 0 to 5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.1 to 2% by weight on a dry weight basis. In some embodiments, the invention comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 10 to 15% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, polymer, *e.g.*, a precipitation inhibitor, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an amount from about 35 to 55% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, microcrystalline cellulose, *e.g.*, microcrystalline cellulose PH 102, *e.g.*, Avicel PH102) in an amount from about 15 to 25% by weight on a dry weight basis, a second pharmaceutically acceptable filler (*e.g.*, lactose, *e.g.*, lactose monohydrate, *e.g.*, FastFlo 316) in an amount from about 15 to 25% by weight on a dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, starch, *e.g.*, modified starch, *e.g.*, sodium starch glycolate) in an amount from about 2.5 to 3.5% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.2 to 1.5% by weight on a dry weight basis. In some embodiments, the oral dosage form is a compressed pharmaceutical tablet or a direct compressed pharmaceutical tablet.

In some embodiments, the excipient is one or more binders (*e.g.*, polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus))). In some embodiments, the binder is a polymer, *e.g.*, a precipitation inhibitor. In some embodiments, the binder comprises two binders (*e.g.*, polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus))). In some embodiments, the binder is a polymer, *e.g.*, a precipitation inhibitor. In some embodiments, the binder is present at about 37.5% weight of binder per weight of the oral dosage form. In some embodiments, the binder is present at about 25% weight of binder per weight of the oral dosage form. In some embodiments, the filler is a polyol (*e.g.*, mannitol-starch (*e.g.*, Pearlitol Flash), mannitol, sorbitol).

In some embodiments, the disintegrant is a polyvinylpolypyrrolidone (*e.g.*, crospovidone). In some embodiments, the disintegrant is present at 0 to 30%, 5 to 25%, 5 to 20%, 5 to 15%, or 10% weight of disintegrant per weight of the oral dosage form.

In an embodiment, an oral dosage form described herein has a greater C_{max} value than a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an admixture. In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.1 times (*e.g.*, at least 1.25 times, at least 1.5 times, at least 2 times, at least 3 times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one aspect, the present invention comprises an oral dosage form comprising: VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride) in an amount from about 10 to 15% by weight on a dry weight basis, a pharmaceutically acceptable excipient (*e.g.*, a binder (*e.g.*, polyvinyl pyrrolidone (*e.g.*, polyvinyl pyrrolidone vinyl acetate copolymer

(PVP/VA), Copovidone))) in an amount from about 15 to 25% by weight on a dry weight basis, a second pharmaceutically acceptable excipient (*e.g.*, a binder (*e.g.*, polyvinylactate (*e.g.*, Soluplus))) in an amount from about 15 to 25% by weight on a dry weight basis, a pharmaceutically acceptable filler (*e.g.*, polyol (*e.g.*, mannitol-starch (*e.g.*, Pearlitol Flash))) in an amount from about 30 to 40% by weight on a dry weight basis, a pharmaceutically acceptable disintegrant (*e.g.*, crospovidone) in an amount from about 5 to 15% by weight on a dry weight basis, and a pharmaceutically acceptable lubricant (*e.g.*, magnesium stearate) in an amount from about 0.2 to 1.5% by weight on a dry weight basis.

In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 10% weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), per weight of the oral dosage form. In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 25% weight of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form. In some embodiments, the VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), is present at 50% weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), per weight of the oral dosage form.

In some embodiments, the physical blend or mixture is provided by a spray dried dispersion process. In some embodiments, the process provides a solid dispersion comprising at least 10% by weight (*e.g.*, 10, 20, 25, 40, 50% or more) of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride). In some embodiments, the process provides a solid dispersion comprising 10% by weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride). In some embodiments, the process provides a solid dispersion comprising 25% by weight of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride). In some embodiments, the dispersion further comprises a polymer, *e.g.*, a polymer matrix (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMACS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M; Hydroxypropyl Methylcellulose Phthalate (HPMCP) or Hypromellose Phthalate, *e.g.*, HPMCP-HP55, HPMCP-HP55S, Methocol E3LV, PVP-VA, Soluplus, PVAP, polymethacrylic acid (*e.g.*, Eudragit, *e.g.*, Eudragit L100-55), Soluplus:PVP-VA mixture, Soluplus, HPMCAS (*e.g.*, HPMCAS-H) mixture). In some embodiments, the dispersion further comprises a polymer matrix (*e.g.*, polymethacrylic acid (*e.g.*, Eudragit, *e.g.*, Eudragit L100-55)).

In one aspect, the present invention comprises an oral dosage form comprising VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), for use

in treating a subject having been identified with a cancer disorder (*e.g.*, mesothelioma (*e.g.*, malignant pleural mesothelioma, *e.g.*, surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.*, triple negative breast cancer), ovarian cancer (*e.g.*, advanced ovarian cancer), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC)), or a non-hematolotic malignancy.

In one aspect, the present invention comprises a method of treating a disorder in a patient in need thereof, the method comprising administering an oral dosage form comprising 10 to 500 mg of VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), to thereby treat the disorder. In some embodiments, the disorder is a cancer disorder (*e.g.*, mesothelioma (*e.g.*, surgical resectable malignant pleural mesothelioma), breast cancer (*e.g.*, triple negative breast cancer, ovarian cancer (*e.g.*, advanced ovarian cancer)), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC)), or a non-hematolotic malignancy.

In some embodiments, the administration is performed in combination with administration of an additional agent (*e.g.*, an anti-cancer or anti-tumor agent, *e.g.*, taxane, *e.g.*, paclitaxel).

In one aspect, the present invention comprises a method for preparing a direct compressed tablet in unit dosage form, which comprises: (a) admixing (*e.g.*, blending) as a % by weight on a dry weight basis: (i) 5 to 50% by weight on a dry weight basis of VS-6063; (ii) a pharmaceutically acceptable excipient (*e.g.*, a binder, *e.g.*, polymer, *e.g.*, a precipitation inhibitor, *e.g.*, HPMC, *e.g.*, HPMC-AS, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF); and (iii) at least one pharmaceutically acceptable excipient selected from a pharmaceutically acceptable filler, a pharmaceutically acceptable disintegrant, and a pharmaceutically acceptable lubricant; to form a VS-6063 formulation in the form of a tabletting powder, capable of being directly compressed into tablets; and (b) compressing the formulation prepared during step (a) to form the compressed VS-6063 tablet in unit dosage form. In some embodiments, a pharmaceutically acceptable filler is present at 30 to 60% by weight on a dry weight basis. In some embodiments, a pharmaceutically acceptable distintegrant is present at 2.5 to 5% by weight on a dry weight basis. In some embodiments, a pharmaceutically acceptable lubricant is present at 0.5 to 2% by weight on a dry weight basis.

In one aspect, the present invention comprises a method of treating a subject having mesothelioma, *e.g.*, malignant pleural mesothelioma, *e.g.*, surgical resectable malignant pleural mesothelioma (*e.g.*, non-metastatic, unresectable), comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject, thereby treating said subject. In some embodiments, the method comprises providing an effective

course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject.

In some embodiments, said subject carries a mutation in a tumor suppressor gene. In some embodiments, said subject carries a mutation in Neurofibromin 2 (NF2). NF2 is a tumor suppressor gene and encodes the protein Merlin, which can function in restricting cellular proliferation and promoting apoptosis. Merlin regulates FAK, at least in part through the attenuation of FAK phosphorylation, which disrupts the ability of FAK to interact with certain binding partners; resulting in the inhibition of FAK mediated signaling pathways. Thus mutations in the NF2 gene which result in decreased expression and/or activity of Merlin, or decreased Merlin expression and/or activity in the absence of NF2 mutations, may lead to increased sensitivity to FAK inhibitors. Therefore cancer patients with one or more alterations in the NF2 gene or an alteration in the level of Merlin expression and/or activity, *e.g.*, decreased level of Merlin expression; may have a cancer characterized by increased sensitivity to FAK inhibitors, and thus may benefit from treatment with a compound as described herein (*e.g.*, VS-6063, *e.g.*, VS-6063 free base, or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride salt)). In some embodiments, said subject has aberrant levels of NF2 and or Merlin, *e.g.*, relative to a reference standard, *e.g.*, a subject without a mutation in a tumor suppressor gene, a subject without a mutation in NF2, or a subject without cancer. In some embodiments, said subject has aberrant levels (*e.g.*, lower levels or dysfunctional levels) of Merlin protein. In some embodiments, the method comprises acquiring, *e.g.*, directly acquiring or indirectly acquiring, information on the NF2 and or Merlin (*i.e.*, Merlin protein) status of the subject. In some embodiments, the NF2 and or Merlin status is determined by immunohistochemistry. In some embodiments, the NF2 and or Merlin status is determined by DNA sequence analysis. In some embodiments, the method comprises testing said subject for NF2 and or Merlin status of the subject. In some embodiments, the method comprises, responsive to NF2 and or Merlin status, *e.g.*, a mutant NF2, administering VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject.

In some embodiments, the level of Merlin expression is low, decreased, or absent. In some embodiments, the level of Merlin expression is compared to a reference standard. In some embodiments, the level of Merlin expression is low, decreased, or absent compared to the reference standard. In some embodiments, the level of Merlin expression is evaluated by the level of Merlin RNA expression. In some embodiments, the level of Merlin expression is measured by the evaluation of the level of RNA that encodes the Merlin. In some embodiments, the level of Merlin expression is evaluated by the level of

Merlin protein expression. In some embodiments, the level of Merlin protein expression is assayed by immunohistochemistry or western blot. Immunohistochemistry or IHC refers to the process of localizing antigens (*e.g.* proteins) in cells of a tissue section exploiting the principle of antibodies binding specifically to antigens in biological tissues. In a preferred embodiment, the level of Merlin protein expression is assayed by immunohistochemistry.

In some embodiments, the patient has one or more alterations in the NF2 gene.

In some embodiments, the alterations in the NF2 gene include mutations, chromosomal deletions, or alterations to the NF2 gene or NF2 promoter. In some embodiments, the alterations to the NF2 promoter include changes in methylation, *e.g.*, hypermethylation. In some embodiments, the evaluation includes acquiring information regarding the NF2 genotype of the patient. In some embodiments, the NF2 genotype of the patient is compared to a reference standard.

In some embodiments, the alterations in the NF2 gene include mutations, chromosomal deletions, or alterations to the NF2 gene. The NF2 gene includes any regulatory sequences, *e.g.*, promoter, and enhancer sequences. In some embodiments, the alterations in the NF2 gene include mutations, chromosomal deletions, or alterations to the NF2 gene. The NF2 gene includes any regulatory sequences, *e.g.*, promoter, and enhancer sequences. In certain embodiments the alteration in the NF2 gene is one or more mutations. In certain embodiments the alteration is a single nucleotide polymorphism. In certain embodiments the alteration is a point mutation. In certain embodiments the alteration is an inactivating mutation. In certain embodiments the alteration in the NF2 gene is a chromosomal deletion. In certain embodiments the alteration is an inactivating chromosomal deletion. In certain embodiments the alteration in the NF2 gene is hypermethylation of the promoter region of the gene.

Cancer patients with one or more alterations in the NF2 gene or an alteration in the level of Merlin expression and/or activity, *e.g.*, decreased level of Merlin expression; may have a cancer characterized by sensitivity or responsiveness to FAK inhibtiors, and thus may benefit from treatment with a FAK inhibitor.

In some embodiments, the method comprises co-administering a course of a second therapy, e.g. a second anti-tumor or anti-cancer therapy, *e.g.*, one or more anti-tumor or anti-cancer agents. In some embodiments, said course of second therapy is provided after a diagnosis of mesothelioma. In some embodiments, the course of second therapy ends prior to initiation of provision of the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises providing a first course of said second therapy; administering VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described

herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); and providing a second course of said second therapy. In some embodiments, the first course is initiated prior to the administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the second course replaces the first course and is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the number of administrations, frequency of administration, amount of second therapeutic agent delivered in an administration, or level of second thereaputic agent in the subject, *e.g.*, in the blood of a subject, is reduced in the second course as compared with the first course. In some embodiments, said second agent is not administered to said subject after the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during a cycle of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said subject has previously received a course of a second therapy, *e.g.*, a second anti-cancer or anti-tumor therapy, *e.g.*, one or more anti-cancer or anti-tumor agents. In some embodiments, said course of second therapy is administered after a diagnosis of mesothelioma. In some embodiments, said course of second therapy ends prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second therapy is not administered after the first administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises providing a second course of said second therapy. In some embodiments, the second course replaces the first course and is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063,

or a pharmaceutically acceptable salt thereof). In some embodiments, the second course is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the number of administrations, frequency of administration, amount of second therapeutic agent delivered in an administration, or level of second therapeutic agent in the subject, *e.g.*, in the blood of a subject, is reduced in the second course as compared with the first course. In some embodiments, said second agent is not administered to said subject after the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during a cycle of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said second therapy comprises the administration of a therapeutic agent, *e.g.*, an anti-tumor or anti-cancer agent. In some embodiments, said second therapy comprises the administration of an additional agent, *e.g.*, an anti-cancer or anti-tumor agent, *e.g.*, an anti-cancer or anti-tumor agent selected from the group comprising mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens. In some embodiments, said therapeutic agent comprises a platin drug, *e.g.*, cisplatin or carboplatin. In some embodiments, said therapeutic agent comprises a drug other than a platin drug, *e.g.*, it comprises a taxane, *e.g.*, docetaxel, paclitaxel; a plant derived anti-tumor substance, *e.g.*, an alkaloid, *e.g.*, vinorelbine; an anti-metabolite, *e.g.*, gemcitabine; or a cytotoxic topoisomerase inhibiting agent, *e.g.*, irinotecan. In some embodiments, said second therapy comprises the administration of a first and a second therapeutic agent. In some embodiments, said the first and the second therapeutic agent is each selected from a group of additional therapeutic agents, *e.g.*, an anti-tumor or anti-cancer agent, *e.g.*, an anti-tumor or anti-cancer agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens. In some embodiments, said therapeutic agent comprises a platin drug, *e.g.*, cisplatin or carboplatin. In some

embodiments, said therapeutic agent comprises a drug other than a platin drug, *e.g.*, it comprises a taxane, *e.g.*, docetaxel, paclitaxel; a plant derived anti-cancer or anti-tumor substance, *e.g.*, an alkaloid, *e.g.*, vinorelbine; an anti-metabolite, *e.g.*, gemcitabine; or a cytotoxic topoisomerase inhibiting agent, *e.g.*, irinotecan.

In one aspect, the present invention comprises a method of treating a subject having cancer, *e.g.*, lung cancer, *e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC, comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject, thereby treating said subject. In some embodiments, the method comprises providing an effective course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); to said subject. In some embodiments, said cancer is metastatic. In some embodiments, the subject has a locally recurrent disease.

In one aspect, the present invention comprises a method of evaluating a subject having cancer, *e.g.*, lung cancer, *e.g.*, non-small cell lung cancer (NSCLC), for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); comprising: acquiring, *e.g.*, directly or indirectly acquiring, the mutation status of a gene in said NSCLC, thereby evaluating said subject. In some embodiments, the gene is selected from the group comprising KRAS, INK4a/Arf, and p53. In some embodiments, the method comprises acquiring the mutation status of KRAS in said NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS and INK4a/Arf in said NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS and p53 in said NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, the method comprises, responsive to said mutation status, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant and a INK4a/Arf mutant, selecting said subject

for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant and a p53 mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant, a INK4a/Arf mutant, and a p53 mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises testing the subject for a mutation in a gene in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation in a gene from the group comprising KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS and INK4a/Arf in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS and p53 in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, a cell of said subject (*e.g.*, a subject having NSCLC) comprises a KRAS mutant; KRAS mutant and INK4a/Arf mutant; or KRAS mutant, INK4a/Arf mutant, and p53 mutant. In some embodiments, the said cancer is metastatic. In some embodiments, the subject has locally recurrent disease.

In some embodiments, the method comprises acquiring mutation status of a gene in said subject's NSCLC. In some embodiments, the gene is selected from the group comprising KRAS, INK4a/Arf, and p53. In some embodiments, the method comprises acquiring the mutation status of KRAS in said subject's NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS and INK4a/Arf in said subject's NSCLC. In some embodiments, the method comprises acquiring the mutation status of subject's KRAS and p53 in said subject's NSCLC. In some embodiments, the method comprises acquiring the mutation status of KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, the method comprises, responsive to said mutation status, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant, selecting said subject for treatment with VS-6063, or a

pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant and a INK4a/Arf mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant and a p53 mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, responsive to a determination that the NSCLC comprises a KRAS mutant, a INK4a/Arf mutant, and a p53 mutant, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises testing the subject for a mutation in a gene in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation in a gene from the group comprising KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, the method comprises directly testing the subject for a mutation of KRAS in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS and INK4a/Arf in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS and p53 in said NSCLC. In some embodiments, the method comprises testing the subject for a mutation of KRAS, INK4a/Arf, and p53 in said NSCLC. In some embodiments, a cell in the subject (*e.g.*, the subject with lung cancer, *e.g.*, NSCLC) comprises a KRAS mutant; KRAS mutant and INK4a/Arf mutant; or KRAS mutant, INK4a/Arf mutant, and p53 mutant.

In some embodiments, the method comprises co-administering a course of a second therapy, e.g. a second anti-tumor or anti-cancer therapy, *e.g.*, one or more anti-tumor or anti-cancer agents. In some embodiments, said course of second therapy is provided after a diagnosis of NSCLC. In some embodiments, the course of second therapy ends prior to initiation of provision of the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises providing a first course of said second therapy; administering VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); and providing a second course of said second therapy. In some embodiments, the first course is initiated prior

to the administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the second course replaces the first course and is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the number of administrations, frequency of administration, amount of second therapeutic agent delivered in an administration, or level of second thereaputic agent in the subject, *e.g.*, in the blood of a subject, is reduced in the second course as compared with the first course. In some embodiments, said second agent is not administered to said subject after the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during a cycle of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said subject has previously received a course of a second therapy, *e.g.*, a second anti-tumor or anti-cancer therapy, *e.g.*, one or more anti-tumor or anti-cancer agents. In some embodiments, said course of second therapy was administered after a diagnosis of NSCLC. In some embodiments, said course of second therapy ends prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second therapy is not administered after the first administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises providing a second course of said second therapy. In some embodiments, the second course replaces the first course and is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the second course is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable

salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the number of administrations, frequency of administration, amount of second therapeutic agent delivered in an administration, or level of second therapeutic agent in the subject, *e.g.*, in the blood of a subject, is reduced in the second course as compared with the first course. In some embodiments, said second agent is not administered to said subject after the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during a cycle of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said second therapy comprises the administration of a therapeutic agent, *e.g.*, an anti-tumor or anti-cancer agent. In some embodiments, said second therapy comprises the administration of and additional agent, *e.g.*, an anti-tumor or anti-cancer agent, *e.g.*, an anti-tumor or anti-cancer agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens. In some embodiments, said therapeutic agent comprises a platin drug, *e.g.*, cisplatin or carboplatin. In some embodiments, said therapeutic agent comprises a drug other than a platin drug, *e.g.*, it comprises a taxane, *e.g.*, docetaxel, paclitaxel; a plant derived anti-tumor substance, *e.g.*, an alkaloid, *e.g.*, vinorelbine; an anti-metabolite, *e.g.*, gemcitabine; or a cytotoxic topoisomerase inhibiting agent, *e.g.*, irinotecan. In some embodiments, said second therapy comprises the administration of a first and a second therapeutic agent. In some embodiments, said the first and the second therapeutic agent is each selected from a group of additional therapeutic agents, *e.g.*, an anti-tumor or anti-cancer agent, *e.g.*, an anti-tumor or anti-cancer agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens. In some embodiments, said therapeutic agent comprises a platin drug, *e.g.*, cisplatin or carboplatin. In some embodiments, said therapeutic agent comprises a drug other than a platin drug, *e.g.*, it comprises a taxane, *e.g.*, docetaxel, paclitaxel; a plant derived anti-tumor or anti-cancer substance, *e.g.*, an alkaloid, *e.g.*,

vinorelbine; an anti-metabolite, *e.g.*, gemcitabine; or a cytotoxic topoisomerase inhibiting agent, *e.g.*, irinotecan.

In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered for a cycle of at least 5, 10, 15, 20, 25, 30 or 35 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered for a cycle of 5 to 40, 10 to 40, 10 to 30, or 10 to 25 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered for a cycle of 15 to 40, 15 to 30, or 15 to 25 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered for a cycle of 21 +/-5, 21 +/-4, 21 +/-3, 21 +/-2, or 21 +/-1 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered for a cycle of 21 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered 1, 2, 3, or 4 times per day. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered 2 times per day. In some embodiments, said VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered orally. In some embodiments, 50 to 800, 50 to 600, 50 to 500, 50 to 400, 50 to 300, or 50 to 200 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered. In some embodiments, 100 to 800, 100 to 600, 100 to 500, 100 to 400, 100 to 300, or 100 to 200 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered. In some embodiments, 200 to 800, 200 to 600, 200 to 500, 200 to 400, or 200 to 300 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof);

is administered. In some embodiments, 250 to 800, 250 to 600, 250 to 500, 250 to 400, or 250 to 300 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered. In some embodiments, the range does not include one or both endpoints, *e.g.*, wherein the range does not include the lower endpoint. In some embodiments, 100 +/- 50, 150 +/- 50, 200 +/- 50, 250 +/- 50, 300 +/- 50, 400 +/- 50, 500 +/- 50, 550 +/- 50 or 600 +/- 50 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered. In some embodiments, 100 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered. In some embodiments, 200 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered. In some embodiments, 400 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); is administered.

In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered in multiple cycles (*e.g.*, more than one cycle). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered in each cycle is constant (*e.g.*, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) administered is the same). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered in a cycle is different than the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in another cycle (*e.g.*, a second cycle). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a cycle is lower than the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition

(*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a subsequent cycle (*e.g.*, a second cycle). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a cycle is greater than the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a subsequent cycle (*e.g.*, a second cycle).

In some embodiments, a unit dosage formulation of 50 +/-25, 100 +/-50, 150 +/-50, 200 +/-50, 250+/-50, 300+/- 50, 400+/-50, 500+/-50, 550+/- 50 or 600+/- 50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 100 +/- 50, 100+/-25, 100+/-10, or 100+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 100+/-20, 100+/-10 or 100+/-5 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 100 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 200 +/- 50, 200+/-25, 200+/-10, or 200+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 200+/-20, 200+/-10 or 200+/-5 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 200 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 400 +/- 50, 400+/-25, 400+/-10, or 400+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 400+/-20, 400+/-10 or

400+/-5 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 400 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered.

In an embodiment, an oral dosage form described herein has a greater C_{max} value than a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an admixture. In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.1 times (*e.g.*, at least 1.25 times, at least 1.5 times, at least 2 times, at least 3 times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure

across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one aspect, the present invention comprises a unit dosage form having 50 to 800 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 50 +/-25 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 50 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the present invention comprises a unit dosage form having 100 to 800 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, the unit dosage form has 400 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In one aspect, the present invention provides a method of treating a subject having ovarian cancer, *e.g.*, advanced or metastatic ovarian cancer, comprising: providing an effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) to said subject, and optionally, providing an effective amount of a second therapeutic agent, *e.g.*, an anti-cancer or anti-tumor agent, *e.g.*, mitotic inhibitor, *e.g.*, a taxane, *e.g.*, paclitaxel, to said subject; said amounts, alone or in combination, being effective to treat said subject, thereby treating said subject, wherein, said subject receives more than 100 or 250 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) for at least one day, *e.g.*, for an entire cycle or course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); said subject receives VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) for at least 5, 10, or 15 days; said second therapeutic agent is provided, *e.g.*, on a different course regimen, *e.g.*, not always on the same day as said VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, providing a course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) to said subject, and optionally, providing a course of a second therapeutic agent, *e.g.*, an anti-cancer or anti-tumor agent, *e.g.*, mitotic inhibitor, *e.g.*, a taxane, *e.g.*, paclitaxel, to said subject, said courses, alone or in combination, being effective to treat said subject.

In one aspect, the present invention provides a method of evaluating a subject having ovarian cancer for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable

salt thereof), comprising: acquiring, e.g. directly acquiring or indirectly acquiring, the mutation status of a gene in said ovarian cancer, thereby evaluating said subject. In some embodiments, the method comprises, responsive to said mutation status, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, testing the subject for a mutation in a gene in said ovarian cancer.

In some embodiments, the method comprises acquiring mutation status of a gene in said subject's ovarian cancer. In some embodiments, the method comprises, responsive to said mutation status, selecting said subject for treatment with VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises testing the subject for a mutation in a gene in said subject's ovarian cancer. In some embodiments, said cancer is metastatic. In some embodiments, said cancer is locally recurrent. In some embodiments, said cancer is advanced.

In some embodiments, the method comprising co-administering a course of a second therapy, e.g. a second anti-cancer or anti-tumor therapy, *e.g.*, one or more anti-cancer or anti-tumor agents. In some embodiments, a course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) and a course of a second therapy, *e.g.*, the administration of an anti-cancer or anti-tumor agent, *e.g.*, mitotic inhibitor, *e.g.*, a taxane, *e.g.*, paclitaxel, are co-administered. In some embodiments, a course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) and a course of a second therapy, *e.g.*, the administration of an anti-cancer or anti-tumor agent, *e.g.*, mitotic inhibitor, *e.g.*, a taxane, *e.g.*, paclitaxel, overlap. In some embodiments, said second therapy comprises the administration of paclitaxel. In some embodiments, said paclitaxel is administered at least twice in a course, *e.g.*, every 7+/-3, 7+/-2, 7+/-1 or 7 days. In some embodiments, said paclitaxel is administered at 80+/-50, 80+/-40, l80+/-30, 80+/-20, 80+/-10, or 80 mg/m^2. In some embodiments, said course of second therapy is provided after a diagnosis of ovarian cancer. In some embodiments, the course of second therapy ends prior to initiation of providing VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof), *e.g.*, a course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some

embodiments, the method comprises, providing a first course of said second therapy; administering VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof); and providing a second course of said second therapy. In some embodiments, the first course is initiated prior to the administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the second course replaces the first course and is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the number of administrations, frequency of administration, amount of second therapeutic agent delivered in an administration, or level of second therapeutic agent in the subject, *e.g.*, in the blood of a subject, is reduced in the second course as compared with the first course. In some embodiments, said second agent is not administered to said subject after the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during the administration of, during the course of administration of, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during a cycle of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said subject has previously received a course of a second therapy, *e.g.*, a second anti-cancer or anti-tumor therapy, *e.g.*, one or more anti-cancer or anti-tumor agents. In some embodiments, said course of second therapy is administered after a diagnosis of ovarian cancer. In some embodiments, said course of second therapy ends prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said second therapy is not administered after the first administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the method comprises, providing a second course of said second therapy. In some

embodiments, the second course replaces the first course and is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the second course is initiated prior to, at the same time as, or after, the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the number of administrations, frequency of administration, amount of second therapeutic agent delivered in an administration, or level of second therapeutic agent in the subject, *e.g.*, in the blood of a subject, is reduced in the second course as compared with the first course. In some embodiments, said second agent is not administered to said subject after the initial administration of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during the course of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, said second agent is not administered to said subject during a cycle of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

In some embodiments, said second therapy comprises the administration of a therapeutic agent, *e.g.*, an anti-cancer or anti-tumor agent. In some embodiments, said therapeutic agent comprises *e.g.*, mitotic inhibitor, *e.g.*, a taxane, *e.g.*, paclitaxel. In some embodiments, said second therapy comprises the administration of a first and a second therapeutic agent. In some embodiments, said second therapy comprises the administration of and additional agent, *e.g.*, an anti-cancer or anti-tumor agent, *e.g.*, an anti-cancer or anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered for a cycle of equal to or greater than 5, 10, 15, 20, 21, 25, 28, 30, 35, 40, 45, or 50 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a

pharmaceutically acceptable salt thereof) is administered for a cycle of 5 to 40, 10 to 40, 10 to 30, or 10 to 25 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered for a cycle of 15 to 40, 15 to 30, or 15 to 25 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered for a cycle of 21 +/-5, 21 +/-4, 21 +/-3, 21 +/-2, or 21 +/-1 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered for a cycle of 21 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered for a cycle of 28 +/-5, 28 +/-4, 28 +/-3, 28 +/-2, or 28 +/-1 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered for a cycle of 28 days. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered 1, 2, 3, or 4 times per day. In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered 2 times per day. In some embodiments, said VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered orally. In some embodiments, 50 to 800, 50 to 600, 50 to 500, 50 to 400, 50 to 300, or 50 to 200 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 100 to 800, 100 to 600, 100 to 500, 100 to 400, 100 to 300, or 100 to 200 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 200 to 800, 200 to 600, 200 to 500, 200 to 400, or 200 to 300 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 250 to 800, 250 to 600, 250 to 500, 250 to 400, or 250 to 300

mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, the range (*e.g.*, a range as described herein) does not include one or both endpoints, *e.g.*, wherein the range does not include the lower endpoint. In some embodiments, 50 +/-25, 100 +/-50, 150 +/-50, 200 +/-50, 250+/-50, 300+/- 50, 400+/-50, 500+/-50, 550+/- 50 or 600+/- 50 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 50 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 100 +/- 50, 100+/-25, 100+/-10, or 100+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 100 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 200 +/- 50, 200+/-25, 200+/-10, or 200+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 200 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 400 +/- 50, 400+/-25, 400+/-10, or 400+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 400 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered.

In some embodiments, VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered in multiple cycles (*e.g.*, more than one cycle). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered in each cycle is constant (*e.g.*, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a

composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) administered is the same). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered in a cycle is different than the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in another cycle (*e.g.*, a second cycle). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a cycle is smaller than the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a subsequent cycle (*e.g.*, a second cycle). In some embodiments, the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a cycle is greater than the amount of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) that is administered in a subsequent cycle (*e.g.*, a second cycle).

In some embodiments, a unit dosage formulation of 50 +/-25, 100 +/-50, 150 +/-50, 200 +/-50, 250+/-50, 300+/- 50, 400+/-50, 500+/-50, 550+/- 50 or 600+/- 50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 200 +/- 50, 200+/-25, 200+/-10, or 200+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 200+/-20, 200+/-10 or 200+/-5 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 200 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 100 +/- 50, 100+/-25, 100+/-10, or 100+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a

pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 100+/-20, 100+/-10 or 100+/-5 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 100 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, 50+/-25, 50+/-10, or 50+/-5 mg/day of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 50+/-20, 50+/-10 or 50+/-5 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered. In some embodiments, a unit dosage formulation of 50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof) is administered.

In an embodiment, an oral dosage form described herein has a greater C_{max} value than a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), in an admixture. In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.1 times (*e.g.*, at least 1.25 times, at least 1.5 times, at least 2 times, at least 3 times, at least 5 times) greater than a reference dosage form of the same dosage amount (*e.g.*, a dosage form having 100 mg of VS-6063 relative to a reference dosage form also having 100 mg of VS-6063). In an embodiment, the C_{max} value of an oral dosage form described herein is at least 1.6 times greater, at least 1.7 times greater, at least 1.8 times greater, at least 1.9 times greater, at least 2 times greater, at least 3 times greater, or at least 4 times greater than a reference dosage form of the same dosage amount.

In an embodiment, an oral dosage form described herein has a reduced food effect relative to a reference oral dosage form, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture. In an embodiment, the difference between the T_{max} value of the fed and fasted states for subjects administered an oral dosage form described herein is less that the difference between the T_{max} value of the fed and fasted states for subjects administered a reference

oral dosage form of the same dosage amount, *e.g.*, a dosage form that does not include an excipient (*e.g.*, a cellulosic polymer and derivatives thereof, *e.g.*, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF) in an admixture.

In an embodiment, an oral dosage form described herein has consistent exposure when administered to a subject. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 50% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount. In an embodiment, an oral dosage form described herein, when administered to a subject, provides an exposure across multiple subjects of less than 40%, 30%, 20%, or 10% of the variability associated with exposure compared with that of a reference oral dosage form of the same dosage amount.

In one aspect, the present invention comprises a unit dosage form having 50 to 800 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 100 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 200 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 +/-50 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 +/-10 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as

described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof). In some embodiments, the unit dosage form has 400 mg of VS-6063, or a pharmaceutically acceptable salt thereof, or composition (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063, or a pharmaceutically acceptable salt thereof).

Detailed Description of the Invention

This disclosure is not limited in its application to the details of the compositions, *e.g.*, formulations, *e.g.*, oral dosage forms, or the specific order of preparation or administration of the composition, *e.g.*, formulations, *e.g.*, oral dosage forms. The compositions, *e.g.*, dosage forms described herein may be suitably prepared using other techniques and/or administered in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting.

Definitions

As used herein, the articles "a" and "an" refer to one or to more than one (*e.g.*, to at least one) of the grammatical object of the article.

"About" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values.

As used herein, an amount of a compound effective to treat a disorder (*e.g.*, a disorder as described herein), "effective amount" or " effective course" refers to an amount of the compound which is effective, upon single or multiple dose administration(s) to a subject, in treating a subject, or in curing, alleviating, relieving or improving a subject with a disorder (*e.g.*, a disorder as described herein) beyond that expected in the absence of such treatment (*e.g.*, placebo treatment).

The term "pharmaceutically acceptable," as used herein, refers to a compound or carrier (*e.g.*, excipient) that may be administered to a subject, together with a compound described herein (*e.g.*, VS-6063, VS-6063 free base, VS-6063 hydrochloride), and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

The term, "pharmaceutically acceptable salts," as used herein, refers to derivatives of a compound described herein (*e.g.*, VS-6063, *e.g.*, VS-6063 free base), wherein the compound is modified by converting an existing acid or base moiety to its salt form (*e.g.*, VS-6063 hydrochloride). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic

residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the disclosure include the conventional non-toxic salts of a compound described herein (*e.g.,* VS-6063), formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the disclosure can be synthesized from a compound described herein (*e.g.,* VS-6063, VS-6063 free base), which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety.

The phrase, "pharmaceutically acceptable derivative or prodrug," as used herein refers to any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound, VS-6063, which, upon administration to a recipient, is capable of providing (directly or indirectly) a therapeutic agent. Particularly favored derivatives and prodrugs are those that increase the bioavailability of a compound described herein (*e.g.,* VS-6063, VS-6063 free base, VS-6063 hydrochloride) when such compounds are administered to a mammal (*e.g.,* by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of a compound described herein (*e.g.,* VS-6063, VS-6063 free base, VS-6063 hydrochloride) to a biological compartment, *e.g.,* relative to a compound described herein (*e.g.,* VS-6063, VS-6063 free base, VS-6063 hydrochloride). Preferred prodrugs include derivatives where a group which enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein.

The term, "oral dosage form," as used herein, refers to a composition or medium used to administer an agent, *e.g.,* VS-6063, to a subject. Typically, an oral dosage form is administered via the mouth, however, "oral dosage form" is intended to cover any substance which is administered to a subject and is absorbed across a membrane, *e.g.,* a mucosal membrane, of the gastrointestinal tract, including, *e.g.,* the mouth, esophagus, stomach, small intestine, large intestine, and colon. For example, "oral dosage form" covers a solution which is administered through a feeding tube into the stomach.

The term, "treat" or "treatment," as used herein, refers to the application or administration of a compound, alone or in combination with, an additional agent to a subject, *e.g.,* a subject who has a disorder (*e.g.,* a disorder as described herein), a symptom of a disorder, or a predisposition toward a disorder, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disorder.

Co-administration, co-administering or co-providing, as used herein in the context of the administration of therapies, refers to administration at the same time, administration of one therapy before (*e.g.*, immediately before, less than 5, 10, 15, 30, 45, 60 minutes; 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 48, 72 or more hours before) administration of a secondary therapy.

Course of therapy, as referred to herein, comprises one or more separate administrations of a therapeutic agent. A course of therapy can comprise one or more cycles of a therapeutic agent.

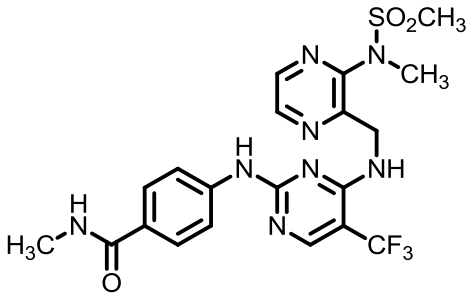
A cycle, as used herein in the context of a cycle of administration of a drug, refers to a period of time for which a drug is administered to a patient. For example, if a drug is administered for a cycle of 21 days, the periodic administration, *e.g.*, daily or twice daily, is given for 21 days. A drug can be administered for more than one cycle. In some embodiments, a first and second or subsequent cycle are the same in terms of one or both of duration and periodic administration. In embodiments, a first and second or subsequent cycle differ in terms of one or both of duration and periodic administration. Rest periods may be interposed between cycles. A rest cycle may be 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 1, 2, 3, 4, 5, 6, 7 days, or 1, 2, 3, 4 or more weeks in length.

Numerous ranges, *e.g.*, ranges for the amount of a drug administered per day, are provided herein. In some embodiments, the range includes both endpoints. In other embodiments, the range excludes one or both endpoints. By way of example, the range can exclude the lower endpoint. Thus, in such an embodiment, a range of 250 to 400 mg/day, excluding the lower endpoint, would cover an amount greater than 250 that is less than or equal to 400 mg/day.

As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human subject having a disorder, *e.g.*, a disorder described herein. The term "non-human animals" of the invention includes all vertebrates, *e.g.*, non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, *e.g.*, sheep, dog, cat, cow, pig, etc.

Compound VS-6063

The active agent (*e.g.*, active ingredient) is the compound VS-6063 (*e.g.*, VS-6063 free base):



or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride), as disclosed in US 7,928,109. VS-6063 is also known as defactinib or PF-04554878.

VS-6063 is a potent inhibitor of the FAK protein tyrosine kinases, and may be adapted to therapeutic use as antiproliferative agents (*e.g.*, anticancer), antitumor (*e.g.*, effective against solid tumors), antiangiogenesis (*e.g.*, stop or prevent proliferation of blood vessels) in mammals, particularly in humans. VS-6063 may be useful in the prevention and treatment of non-hematolotic malignancies. Moreover, VS-6063 may be useful in the prevention and treatment of a variety of human hyperproliferative disorders such as malignant and benign tumors of the liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, head and neck, and other hyperplastic conditions such as benign hyperplasia of the skin (*e.g.*, psoriasis) and benign hyperplasia of the prostate (*e.g.*, BPH). VS-6063 may also be useful in the prevention and treatment of disorders such as mesothelioma.

In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in the amount of 5, 10, 11, 12, 12.5, 13, 14, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60% w/w or greater. In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in the amount of about 10 to 50% w/w. In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in the amount of about 10% w/w. In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in greater than 10% w/w. In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in the amount of about 13% w/w. In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in the amount of about 25% w/w. In some embodiments, VS-6063 or a pharmaceutically acceptable salt thereof is present in the composition in the amount of about 50% w/w.

Pharmaceutical compositions and oral dosage forms

Pharmaceutical compositions are provided which may, for example, be in a form suitable for oral administration such as a tablet, capsule, pill, powder, sustained release formulations, solution, and suspension. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. Pharmaceutical compositions may comprise, in addition to VS-6063 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and may optionally further comprise one or more pharmaceutically acceptable excipients, such as, for example, stabilizers (*e.g.*, a binder, *e.g.*, polymer, *e.g.*, a precipitation inhibitor, for example, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or

Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M)), diluents, binders, and lubricants. In some embodiments, the composition provides a free-flowing, cohesive, tableting powder, capable of being directly compressed into a tablet. In addition, the tablet may include other medicinal or pharmaceutical agents, carriers, and or adjuvants. Exemplary pharmaceutical compositions include compressed tablets (*e.g.*, directly compressed tablets), *e.g.*, comprising VS-6063 or a pharmaceutically acceptable salt thereof.

Tablets are also provided comprising the active or therapeutic ingredient (*e.g.*, a compound described herein, *e.g.*, VS-6063 (*e.g.*, VS-6063 free base), or a pharmaceutically acceptable salt thereof (*e.g.*, VS-6063 hydrochloride)). In addition to the active or therapeutic ingredients, tablets may contain a number of inert materials such as carriers. Pharmaceutically acceptable carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, sesame oil and the like. Saline solutions and aqueous dextrose can also be employed as liquid carriers. Oral dosage forms for use in accordance with the present invention thus may be formulated in conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations which, can be used pharmaceutically.

Excipients can impart good powder flow and compression characteristics to the material being compressed. Desirable characteristics of excipients can include high-compressibilities as to allow for strong tablets to be made at low compression forces; good powder flow properties that can improve the powder flow of other excipients in the composition; and cohesiveness, for example to prevent a tablet from crumbling during processing, shipping, and handling. Such properties are imparted to these excipients through pretreatment steps, such as dry granulation (*e.g.*, by roller compaction, slugging), wet granulation, spray drying spheronization (*e.g.*, spray dried dispersion, solid nanodispersions) or crystallization (*e.g.*, salt forms) of a pharmaceutical composition. They may be classified according to the role that they play in the final tablet. Some excipients can serve multiple functions. For example, a filler can be a binder and or serve as a precipitation inhibitor. Other excipients which give physical characteristics to a finished tablet are coloring and flavoring agents (*e.g.*, in the case of chewable tablets). Examples of excipients are described, for example, in the Handbook of Pharmaceutical Excipients (5^{th} edition), Edited by Raymond C Rowe, Paul J. Sheskey, and Sian C. Owen; Publisher: Pharmaceutical Press.

For oral administration, the active ingredients, *e.g.*, the compounds described herein (*e.g.*, VS-6063, *e.g.*, VS-6063 free base or VS-6063 hydrochloride), can be formulated readily by combining the active ingredients with pharmaceutically acceptable carriers well known in the art. Such carriers enable

the active ingredients of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, powders or granules, suspensions or solutions in water or non-aqueous media, and the like, for oral ingestion by a subject. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain, for example, tablets. Suitable excipients such as diluents, binders or disintegrants may be desirable.

Tablets typically contain diluents or fillers, which are added, for example, to increase the bulk weight of the blend resulting in a practical size for compression. Diluents or fillers that may be used include one or more of calcium salts such as calcium phosphate dibasic and sugars such as lactose, sucrose, dextrose, microcrystalline cellulose, mannitol, and maltodextrin. Examples of pharmaceutically acceptable fillers and pharmaceutically acceptable diluents include, but are not limited to, confectioner's sugar, compressible sugar, dextrates, dextrin, dextrose, lactose, mannitol, microcrystalline cellulose, powdered cellulose, sorbitol, sucrose and talc. In some embodiments, the diluent or filler is microcrystalline cellulose, which can be manufactured by the controlled hydrolysis of alpha-cellulose. Suitable microcrystalline cellulose will have an average particle size of from about 20 nm to about 200 nm. Suitable microcrystalline cellulose includes Avicel PH 101, Avicel PH 102, Avicel PH 103, Avicel PH 105 and Avicel PH 200, *e.g.*, manufactured by FMC Corporation. In some embodiments, the diluents or filler is lactose. In some embodiments, the lactose has an average particle size of between about 50 μm and about 500 μm prior to formulating.

The pharmaceutical composition will generally also include a lubricant. Lubricants are typically added to prevent the tabletting materials from sticking to punches, minimize friction during tablet compression, and to allow for removal of the compressed tablet from the die. Such lubricants are commonly included in the final tablet mix in amounts usually less than 1% by weight per weight of a composition. Examples of lubricants include, but are not limited to, colloidal silica, magnesium trisilicate, talc, magnesium carbonate, magnesium oxide, glycerylbehaptate, polyethylene glycol, ethylene oxide polymers (*e.g.*, Carbowax), sodium lauryl sulphate, magnesium stearate, aluminum stearate, calcium stearate, sodium stearyl fumarate, stearic acid, magnesium lauryl stearate, and mixtures of magnesium stearate with sodium lauryl sulphate. Preferred lubricants include calcium stearate, magnesium stearate and sodium stearyl fumarate. In some embodiments, the lubricant is magnesium stearate. In some embodiments, the amount of lubricant employed is from about 0.1 to about 2.0%, preferably about 0.5 to 1.5% w/w.

Glidants are substances added to a powder that can improve its flowability. Examples of glidants include magnesium stearate, colloidal silicon dioxide (such as the grades sold as Aerosil), starch and talc.

Glidants may be present in the pharmaceutical composition at a level of from 0 to about 5% w/w. Again, it should be noted that excipients may serve multiple functions. The lubricant, for example magnesium stearate, may also function as a glidant.

In addition to the diluent(s)/filler(s) and lubricant(s), other conventional excipients may also be present in the pharmaceutical compositions of the invention. Such additional excipients include disintegrants, binders, flavouring agents, colours and glidants. Some excipients can serve multiple functions, for example as both binder and tablet disintegrant.

A tablet disintegrant may be present in an amount necessary to expedite dissolution (*e.g.*, increase the rate of tablet disintegration). Disintegrants are excipients which can oppose the physical forces of particle bonding in a tablet or capsule when the dosage form is placed in an aqueous environment. Disintegrants include starch derivatives and salts of carboxymethylcellulose. Examples of pharmaceutically acceptable disintegrants include, but are not limited to, starches, *e.g.*, sodium starch glycolate, pregelatinized starch; clays; celluloses; alginates; gums; cross-linked polymers, *e.g.*, cross-linked polyvinyl pyrrolidone (*e.g.*, polyvinyl polypyrrolidone, PVPP, crospovidone, crospolividone), cross-linked calcium carboxymethylcellulose and cross-linked sodium carboxymethylcellulose (sodium croscarmellose); and soy polysaccharides. In some embodiments, the disintegrant used in the composition is sodium starch glycolate. Generally the amount of disintegrant can be from 0 to about 25% w/w, more commonly from about 1% to about 15% w/w, and usually less than 15%, less than 10%, or less than 5% w/w, of the composition. In some embodiments, the amount of disintegrant is about 10% w/w of the composition. In some embodiments, the amount of disintegrant is about 3% w/w of the composition.

Binders are excipients which contribute to particle adhesion in a solid formulation. Examples of binders include, but are not limited to, polymers, *e.g.*, starches (*e.g.*, mannitol-starch, *e.g.*, Pearlitol Flash); corn syrup; polysaccharides; gelatin; celluloses and derivatives thereof, *e.g.*, microcrystalline cellulose, carboxymethylcellulose, Hydroxypropyl Methylcellulose (HPMC) or Hypromellose (*e.g.*, Hydroxypropyl Methylcellulose Acetate Succinate (HPMC-AS) or Hypromellose Acetate Succinate, *e.g.*, HPMCAS-H, HPMCAS-M, HPMCAS-HF), HPMC phthalate (HPMCP), (*e.g.*, HPMCP-HP55, HPMCP-HP55S), Methocel (*e.g.*, Methocel E3LV)), hydroxypropyl cellulose, hydroxyethylcellulose, ethylcellulose, microcrystalline cellulose; and sugars such as lactose, sucrose, dextrose, glucose, maltodextrin, mannitol, xylitol; polymethacrylates (*e.g.*, Eudragit, *e.g.*, Eudragit L100-55), polyvinyl pyrrolidone (*e.g.*, polyvinyl pyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate (*e.g.*, polyvinyl phthalate (PVAP); polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft

copolymer, Soluplus)), sorbitol, pregelatinized starch, alginic acids, and salts thereof such as sodium alginate, magnesium aluminum silicate, polyethylene glycol, and the like. Generally, the amount of binder can vary widely, e.g. from 0% to 95% w/w of the composition. As noted above, excipients may serve multiple functions. For instance, the tabletting diluent may also serve as a binder. In some embodiments, the binder is a precipitation inhibitor. A precipitation inhibitor is generally an excipient that mediates supersaturation stabilization (*e.g.*, stabilization of a supersaturated solution) and or slows and or inhibits (*e.g.*, prevents rapid) precipitation, *e.g.*, in solution or in the GI tract. In some embodiments, the binder is selected from the group consisting of: starches (*e.g.*, mannitol-starch, *e.g.*, Pearlitol Flash); celluloses and derivatives thereof, *e.g.*, microcrystalline cellulose, carboxymethylcellulose, hydroxypropyl methylcellulose (HPMC) (*e.g.*, HPMC acetate succinate (HPMCAS), (*e.g.*, HPMCAS-H, HPMCAS-M), HPMC phthalate (HPMCP), (*e.g.*, HPMCP-HP55, HPMCP-HP55S), Methocel (*e.g.*, Methocel E3LV)), hydroxypropyl cellulose, hydroxyethylcellulose, ethylcellulose, microcrystalline cellulose; and sugars such as lactose, sucrose, dextrose, glucose, maltodextrin, mannitol, xylitol; polymethacrylates (*e.g.*, Eudragit, *e.g.*, Eudragit L100-55), polyvinyl pyrrolidone (*e.g.*, polyvinyl pyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone), other copolymers (*e.g.*, comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus)). In some embodiments, the binder is polyvinylpyrrolidone (*e.g.*, polyvinylpyrrolidone vinyl acetate copolymer (PVP/VA), Copovidone). In some embodiments, the binder is mannitol-starch, *e.g.*, Pearlitol Flash. In some embodiments, the binder is a copolymer (*e.g.*, a copolymer comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylactate (*e.g.*, Soluplus). In some embodiments, the binder is a polymer. In some embodiments, the polymer is a precipitation inhibitor. In some embodiments, the precipitation inhibitor is a HPMC (*e.g.*, HPMCAS, *e.g.*, HPMCAS-H, HPMCAS-M, or HPMCAS-HF).

In some embodiments, more than one binder is used in the composition. In some embodiments, the amount of binder is from about 0 to 60% w/w of the composition. In some embodiments, the amount of binder present in the composition is 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80% or greater weight per weight of composition. In some embodiments, the amount of binder is about 20 to about 80% w/w of the composition. In some embodiments, the amount of binder is about 50% w/w of the composition. In some embodiments, the amount of binder is about 80% w/w of the composition.

The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics"). Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens 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 status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Tablets may be plain, film, or sugar coated bisected, embossed, layered, or sustained-release. They can be made in a variety of sizes, shapes, and colors. Tablets may be swallowed, chewed, or dissolved in the buccal cavity or beneath the tongue.

Three processes are generally used for making compressed tablets: wet granulation, direct compression and dry granulation. The method of preparation and type of excipients are selected to give the tablet formulation the desired physical characteristics that allow for the rapid compression of the tablets. After compression, the tablets must have a number of additional attributes, such as appearance, hardness, disintegrating ability and an acceptable dissolution profile. Choice of fillers and other excipients will depend on the chemical and physical properties of the drug, behavior of the mixture during processing and the properties of the final tablets. Preformulation studies are done to determine the chemical and physical compatibility of the active component with proposed excipients.

Direct compression is a relatively quick process where powdered materials are compressed directly without changing the physical and chemical properties of the drug. The active ingredient(s) (*e.g.*, a compound as described herein, *e.g.*, VS-6063, *e.g.*, VS-6063 free base or VS-6063 hydrochloride), direct compression excipients and other auxiliary substances, such as a glidant and lubricant are blended (*e.g.*, in a twin shell blender or similar low shear apparatus) before being compressed into tablets. The method typically consists of blending of the ingredients, dry screening, lubrication and compression.

The dry granulation method may be used where one of the constituents, either the drug or the diluent, has sufficient cohesive properties to be tableted. The method consists of blending, slugging (or roller compaction of) the ingredients, dry screening, lubrication and compression. In some embodiments, dry granulation is used to improve *e.g.*, processibility, *e.g.*, flow properties of the blend (*e.g.*, a composition as described herein, *e.g.*, a composition comprising VS-6063).

The wet granulation method may be used to, *e.g.*, convert a powder mixture into granules having improved flow and cohesive properties for tableting. The procedure consists of mixing the powders, *e.g.*, in a suitable blender followed by adding the granulating solution under shear to the mixed powders to obtain a granulation. The damp mass is then screened through a suitable screen and dried by tray drying or fluidized bed drying. Alternately, the wet mass may be dried and passed through a mill. The overall process includes weighing, dry powder blending, wet granulating, drying, milling, blending lubrication and compression.

Oral dosage forms may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert.

Methods of treatment and administration

The present invention relates to, *inter alia*, methods for treating abnormal cell growth, *e.g.*, cancer, comprising administering an oral dosage form comprising VS-6063, or a pharmaceutically acceptable salt thereof.

Abnormal cell growth

Abnormal cell growth, as used herein and unless otherwise indicated, refers to cell growth that is independent of normal regulatory mechanisms (*e.g.*, loss of contact inhibition). This includes the abnormal growth of: (1) tumor cells (tumors) that proliferate for example by expressing a mutated tyrosine kinase or overexpression of a receptor tyrosine kinase; (2) benign and malignant cells of other proliferative diseases for example in which aberrant tyrosine kinase activation occurs; (3) any tumors that proliferate for example by receptor tyrosine kinases; (4) any tumors that proliferate for example by aberrant serine/threonine kinase activation; and (5) benign and malignant cells of other proliferative diseases for example in which aberrant serine/threonine kinase activation occurs. Abnormal cell growth can refer to cell growth in epithelial (*e.g.*, carcinomas, adenocarcinomas); mesenchymal (*e.g.*, sarcomas (e.g. leiomyosarcoma, Ewing's sarcoma)); hematopoetic (*e.g.*, lymphomas, leukemias, myelodysplasias (*e.g.*, pre-malignant)); or other (*e.g.*, melanoma, mesothelioma, and other tumors of unknown origin) cells.

Abnormal cell growth can refer to cancer, which includes, but is not limited to, lung cancer (*e.g.*, non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC; metastatic cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer (*e.g.*, advanced or metastatic ovarian cancer), rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer (*e.g.*, triple-negative breast cancer (*e.g.*, breast cancer

which does not express the genes for the estrogen receptor, progesterone receiptor, and Her2/neu)), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, mesothelioma (*e.g.*, malignant pleural mesothelioma, *e.g.*, surgical resectable malignant pleural mesothelioma) or a combination of one or more of the foregoing cancers. In some embodiments, the cancer is metastatic. In some embodiments, the abnormal cell growth is locally recurring (*e.g.*, the subject has a locally recurrent disease, *e.g.*, cancer).

In some embodiments, the method comprises administering to a mammal an oral dosage form of the invention that is effective in treating non-hematolotic malignancies. In some embodiments, the method is effective in treating breast, lung, and ovarian cancer. In an embodiment, the breast cancer is triple-negative breast cancer (*e.g.*, breast cancer which does not express the genes for the estrogen receptor, progesterone receiptor, and Her2/neu). In an embodiment, the lung cancer is non-small cell lung cancer (NSCLC), *e.g.*, KRAS mutant NSCLC. In an embodiment, the ovarian cancer is advanced ovarian cancer (*e.g.*, advanced ovarian cancer or metastatic ovarian cancer).

In an embodiment, the method comprises administering a mammal a composition, *e.g.*, an oral dosage form of the invention that is effective in treating mesothelioma (*e.g.*, malignant pleural mesothelioma, *e.g.*, surgical resectable malignant pleural mesothelioma).

Inventive methods of the present invention contemplate single as well as multiple administrations of a therapeutically effective amount of a composition as described herein. Compositions, *e.g.*, a composition as described herein, can be administered at regular intervals, depending on the nature, severity and extent of the subject's condition. In some embodiments, a composition described herein is administered in a single dose. In some embodiments, a composition described herein is administered in multiple doses. In some embodiments, a therapeutically effective amount of a composition, *e.g.*, a composition as described herein, may be administered orally and periodically at regular intervals (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times every 1, 2, 3, 4, 5, or 6 days, or every 1, 2, 3, 4, 5, 6, 7, 8, or 9 weeks, or every 1, 2, 3, 4, 5, 6, 7, 8, 9 months or longer).

In some embodiments, a compositions described herein is administered at a predetermined interval (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times every 1, 2, 3, 4, 5, or 6 days, or every 1, 2, 3, 4, 5, 6, 7, 8, or 9 weeks, or every 1, 2, 3, 4, 5, 6, 7, 8, 9 months or longer).

Combinations

The oral dosage forms and methods of the present invention may be administered in combination with an additional (*e.g.*, a second, secondary) agent (*e.g.*, therapeutic agent). The additional agent can include an anti-tumor or anti-cancer agent, *e.g.*, an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.

An oral dosage form of the invention may be applied as a sole therapy or may involve one or more other anti-tumor substances, for example those selected from, for example, mitotic inhibitors, for example taxanes, *e.g.*, docetaxel (Taxotere), paclitaxel; alkaloids, *e.g.*, vinblastine; alkylating agents, for example platinum-coordinated alkylating compounds, *e.g.*, platins, *e.g.*, cis-platin, oxaliplatin, and carboplatin; and cyclophosphamide; anti-metabolites, for example gemcitabine, 5-fluorouracil, capecitabine, cytosine arabinoside and hydroxyurea, growth factor inhibitors; cell cycle inhibitors; intercalating antibiotics, for example adriamycin and bleomycin; enzymes, for example interferon; and anti-hormones, for example anti-estrogens such as Nolvadex (tamoxifen) or, for example anti-androgens such as Casodex (4′-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3′-(trifluoromethyl)propionanilide).

An oral dosage form of the invention may be used alone or in combination with one or more of a variety of anti-cancer agents or supportive care agents. For example, the oral dosage forms of the invention may be used with cytotoxic agents, *e.g.*, one or more selected from the group consisting of a camptothecin, irinotecan HCl (Camptosar), edotecarin, SU-11248, epirubicin (Ellence); taxanes, *e.g.*, docetaxel (Taxotere), paclitaxel; rituximab (Rituxan) bevacizumab (Avastin), imatinib mesylate (Gleevac), Erbitux, gefitinib (Iressa), and combinations thereof. The invention also contemplates the use of the oral dosage forms of the invention together with hormonal therapy, *e.g.*, exemestane (Aromasin), Lupron, anastrozole (Arimidex), tamoxifen citrate (Nolvadex), Trelstar, and combinations thereof. Further, the invention provides an oral dosage forms of the invention alone or in combination with one or more supportive care products, *e.g.*, a product selected from the group consisting of Filgrastim (Neupogen), ondansetron (Zofran), Fragmin, Procrit, Aloxi, Emend, or combinations thereof. Such

conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment.

Oral dosage forms of the invention may be used with the following, which is a non-limiting list of examples of additional or secondary agents, *e.g.*, anti-tumor agents, anti-cancer agents, that may be used with the oral dosage forms of the invention.

- **Alkylating agents** include, but are not limited to, nitrogen mustard N-oxide, cyclophosphamide, ifosfamide, melphalan, busulfan, mitobronitol, carboquone, thiotepa, ranimustine, nimustine, temozolomide, AMD-473, altretamine, AP-5280, apaziquone, brostallicin, bendamustine, carmustine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, mafosfamide, and mitolactol; platinum-coordinated alkylating compounds, *e.g.*, platins, such as cisplatin, carboplatin, eptaplatin, lobaplatin, nedaplatin, oxaliplatin or satrplatin;
- **Anti-metabolites** include but are not limited to, methotrexate, 6-mercaptopurine riboside, mercaptopurine, gemcitabine, 5-fluorouracil (5-FU) alone or in combination with leucovorin, tegafur, UFT, doxifluridine, carmofur, cytarabine, cytarabine ocfosfate, enocitabine, S-1, gemcitabine, fludarabin, 5-azacitidine, capecitabine, cladribine, clofarabine, decitabine, eflornithine, ethynylcytidine, cytosine arabinoside, hydroxyurea, TS-1, melphalan, nelarabine, nolatrexed, ocfosfate, disodium premetrexed, pentostatin, pelitrexol, raltitrexed, triapine, trimetrexate, vidarabine, vincristine, vinorelbine;
- **Antibiotics** include but are not limited to: aclarubicin, actinomycin D, amrubicin, annamycin, bleomycin, daunorubicin, doxorubicin, elsamitrucin, epirubicin, galarubicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin or zinostatin;
- **Hormonal therapy agents**, *e.g.*, exemestane (Aromasin), Lupron, anastrozole (Arimidex), doxercalciferol, fadrozole, formestane, anti-estrogens such as tamoxifen citrate (Nolvadex) and fulvestrant, Trelstar, toremifene, raloxifene, lasofoxifene, letrozole (Femara), or anti-androgens such as bicalutamide, flutamide, mifepristone, nilutamide, Casodex® (4′-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3′-(trifluoromethyl)propionanilide) and combinations thereof;
- **Plant derived anti-tumor substances** include for example those selected from mitotic inhibitors, for example alkaloids, *e.g.*, vinblastine; taxanes, *e.g.*, docetaxel (Taxotere), paclitaxel;

- **Cytotoxic topoisomerase inhibiting agents** include one or more agents selected from the group consisting of aclarubicin, amonafide, belotecan, camptothecin and camptothecin derivatives, including but are not limited to 10-hydroxycamptothecin, 9-aminocamptothecin, diflomotecan, irinotecan, irinotecan HCl (Camptosar), edotecarin, epirubicin (Ellence), etoposide, exatecan, gimatecan, lurtotecan, mitoxantrone, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, and topotecan, and combinations thereof;
- **Immunologicals** include interferons and numerous other immune enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a or interferon gamma-n1. Other agents include filgrastim, lentinan, sizofilan, TheraCys, ubenimex, WF-10, aldesleukin, alemtuzumab, BAM-002, dacarbazine, daclizumab, denileukin, gemtuzumab ozogamicin, ibritumomab, imiquimod, lenograstim, lentinan, melanoma vaccine (Corixa), molgramostim, OncoVAX-CL, sargramostim, tasonermin, tecleukin, thymalasin, tositumomab, Virulizin, Z-100, epratuzumab, mitumomab, oregovomab, pemtumomab, and Provenge;
- **Biological response modifiers** are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity. Such agents include krestin, lentinan, sizofuran, picibanil, or ubenimex;
- **Other anticancer agents** include alitretinoin, ampligen, atrasentan, bexarotene, bortezomib, Bosentan, calcitriol, exisulind, finasteride, fotemustine, ibandronic acid, miltefosine, mitoxantrone, 1-asparaginase, procarbazine, dacarbazine, hydroxycarbamide, pegaspargase, pentostatin, tazarotene, TLK-286, Velcade, Tarceva, tretinoin, CTLA4 inhibitors, or a farnesyl protein transferase inhibitors;
- **Other anti-angiogenic compounds** include acitretin, fenretinide, thalidomide, zoledronic acid, angiostatin, aplidine, cilengtide, combretastatin A-4, endostatin, halofuginone, rebimastat, removab, Revlimid, squalamine, ukrain and Vitaxin;
- **Platinum-coordinated compounds** include but are not limited to, cisplatin, carboplatin, nedaplatin, or oxaliplatin;
- **Tyrosine kinase inhibitors** are Iressa or SU5416;
- **Antibodies** include Herceptin, Erbitux, Avastin, Rituximab, or a cytotoxic lymphocyte antigen 4 (CTLA4); and

- **Interferons** include interferon alpha, interferon alpha-2a, interferon, alpha-2b, interferon beta, interferon gamma-1a or interferon gamma-n1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows exemplary mean dissolution profiles of 100mg VS-6063 IR tablet formulations

FIG. 2 shows exemplary mean dissolution profiles of 100mg VS-6063 IR tablet formulations

FIG. 3 shows exemplary mean dissolution profiles of 100mg VS-6063 IR tablet formulations

FIG. 4 shows exemplary mean dissolution profiles of 100mg VS-6063 IR tablet formulations in 0.1M HCl

FIG. 5 shows exemplary mean (n=4) VS-6063 Concentrations in Plasma Following an Oral Gavage Dose of VS-6063 in Various Formulations to Male Beagle Dogs at 10 mg API/kg - Rectilinear Scale

FIG. 6 shows exemplary mean (n=4) VS-6063 Concentrations in Plasma Following an Oral Gavage Dose of VS-6063 in Various Formulations to Male Beagle Dogs at 10 or 20 mg API/kg - Rectilinear Scale

EXAMPLES

The disclosure is further described in the following examples, which do not limit the scope of the claims.

Example 1. Dry Granulation of VS-6063 formulations

VS-6063 immediate release (IR) formulations were prepared using a dry granulation approach. The composition of the formulations is shown on **Table 1**:

Table 1: Composition of 100mg VS-6063 IR tablet formulation

Composition	HPMC-AS Formulation			PVP VA/Soluplus Forumlation		
	% w/w	mg/tablet	g/per 200g batch	% w/w	mg/tablet	g/per 200g batch
Intragranular blend						
VS-6063* (free base)	13.529	108.23 (100.00)	27.058	13.529	108.23 (100.00)	27.058
HPMC AS-HF	40.586	324.69	81.172	–	–	–
PVP VA	–	–	–	20.293	162.35	40.586
Soluplus	–	–	–	20.293	162.35	40.586
Avicel PH 102	20.943	167.54	41.886	–	–	–
Lactose Monohydrate (FastFlo 316)	20.943	167.54	41.886	–	–	–

Pearlitol® Flash	–	–	–	34.885	279.08	69.770
Crospovidone	–	–	–	10.000	80.00	20.000
Sodium starch glycolate	3.000	24.00	6.000	–	–	–
Magnesium Stearate	0.500	4.00	1.000	0.500	4.00	1.000
Sub-total	**99.50**	**796.00**	**199.00**	**99.50**	**796.01**	**199.00**
Extragranular blend						
Magnesium stearate	0.500	4.00	Final blend for tableting based on yield of granulate available	0.500	4.00	Final blend for tableting based on yield of granulate available
Total	**100.00**	**800.00**		**100.00**	**800.00**	

The intragranular blend was prepared by screening VS-6063 and all excipients through 600µm sieves before use. The required amount of the functional excipients and VS-6063 was weighed out and pre-blended for 1 minute using a large plastic spatula, followed by mixing on the Turbula mixer at a setting of 32rpm for 5 minutes. The remaining screened components (except the magnesium stearate) were added to the pre-blend mixed for 1 minute using a large plastic spatula, followed by mixing on the Turbula mixer at a setting of 32rpm for 15 minutes. Final blending on the Turbula mixer was conducted at a setting of 32rpm for 3 minutes after addition of magnesium stearate. The intragranular blend was then roller compacted. The granule properties for two IR tablet formulations were characterized and compared to the direct compression batch of the same composition; shown in **Table 2:**

Table 2: Powder characterisation for 100mg VS-6063 tablet formulations

Test	HPMC-AS Dry granulation	HPMC-AS Direct Compression	PVP VA/Soluplus Dry granulation	PVP VA/Soluplus Direct Compression
Bulk Density (g/mL)	0.522	0.282	0.572	Not tested
Tapped Density (g/mL)	0.679	0.570	0.748	Not tested
Hausner Ratio	1.30	2.02	1.31	Not tested
Carr's Index (%)	23.20	50.60	23.49	Not tested
Angle of Repose (°)	17.54	38.37	36.49	Not tested

The particle size analysis data indicate bi-modal particle size distribution with approximately 20% of the particle size distribution >710µm and approximately 20% of the particle size distribution < 75µm.

The physical properties of the blends were determined and compared to the direct compression formulation (HPMC-AS formulation only); (**Table 2**). The Hausner ratio for the blends tested was >1.3 and the Carr's index was **>23**% indicating the blends may have poor powder flow, cohesiveness and high interparticulate friction. However, the angle of repose does indicate passable powder flow.

In comparison to a direct compression approach, a higher compression force may be required to achieve the desired tablet hardness for the dry granulated blends.

Table 3: Tablet compression data for 100mg VS-6063 tablet formulations

Test	HPMC-AS Dry granulation	HPMC-AS Direct Compression	PVP VA/Soluplus Dry granulation	PVP VA/Soluplus Direct Compression
Average Hardness (kP)	12.7 %RSD 8.7 Min 11.9 Max 14.0	13.3 %RSD 3.8 Min 12.8 Max 14.1	11.7 %RSD 8.8 Min 10.4 Max 12.7	11.2
Average Tablet Weight (mg)	805.4 %RSD 0.9 Min 797.8 Max 821.6	804.7 %RSD 0.7 Min 796.7 Max 814.4	793.0 %RSD 2.1 Min 763.9 Max 810.2	797.1 %RSD 0.5 Min 791.2 Max 803.2
Average Tablet Thickness (mm)	5.6 %RSD 0.3 Min 5.5 Max 5.6	6.2 %RSD 0.6 Min 6.2 Max 6.3	5.4 %RSD 1.7 Min 5.2 Max 5.5	5.6 %RSD 0.4 Min 5.6 Max 5.6
Compression Force (lbs)	1800	800	10000	3500
Disintegration time (mins)	10.5	8*	20	8

Figure 1 shows that for the HPMC-AS formulation, dry granulation may slow dissolution after a pH switch (*e.g.*, gastric to intestinal pH) in comparison to the dissolution of tablets prepared using a direct compression approach.

For the PVP VA/Soluplus formulation, the dissolution profiles for tablets prepared via a dry granulation approach may be slower in comparison to tablets prepared using a direct compression approach. The dissolution profile generated was very similar to that for a VS-6063 reference product (*e.g.*, unformulated product).

Example 2. Dry Granulation of VS-6063 immediate release formulations

One batch of the VS-6063 IR formulations was prepared (**Table 4**), using a dry granulation approach:

Table 4: Composition of 100mg VS-6063 tablet formulations

Composition	PVP VA/Soluplus		
	% w/w	mg/tablet	g/per 200g batch
Intragranular blend			
VS-6063* (free base)	13.529	108.23 (100.00)	27.058
PVP VA	20.293	162.35	40.586
Soluplus	20.293	162.35	40.586
Pearlitol® Flash	34.885	279.08	69.770
Crospovidone	10.000	80.00	20.000
Magnesium Stearate	0.500	4.00	1.000
Sub-total	**99.50**	**796.01**	**199.00**
Extragranular blend			
Magnesium stearate	0.500	4.00	Final blend for tableting based on yield of granulate available
Total	**100.00**	**800.00**	

The intragranular blend was prepared by screening VS-6063 and all excipients through 600µm sieves before use. The required amount of the functional excipients and VS-6063 was weighed out and pre-blended for 1 minute using a large plastic spatula, followed by mixing on the Turbula mixer at a setting of 32rpm for 5 minutes. The remaining screened components (except the magnesium stearate) were added to the pre-blend, mixed for 1 minute using a large plastic spatula, followed by mixing on the Turbula mixer at a setting of 32rpm for 15 minutes. Final blending on the Turbula mixer was conducted at a setting of 32rpm for 3 minutes after addition of magnesium stearate. The intragranular blend was then roller compacted.

After completion of the dry granulation process, the compacted ribbons were passed through 1.4mm, 1.18mm and 850µm sieves. The tablet blend was then prepared by mixing the granules with magnesium stearate using the Turbula mixer at 32rpm for 3 minutes.

Table 5: Powder characterisation for 100mg VS-6063 tablet formulations

Test	PVP VA/Soluplus Prior to dry granulation	PVP VA/Soluplus Dry granulation softer ribbons	PVP VA/Soluplus Dry granulation harder ribbons
Bulk Density (g/mL)	0.431	0.529	0.572
Tapped Density (g/mL)	0.610	0.761	0.748

Test	PVP VA/Soluplus Prior to dry granulation	PVP VA/Soluplus Dry granulation softer ribbons	PVP VA/Soluplus Dry granulation harder ribbons
Hausner Ratio	1.41	1.44	1.31
Carr's Index (%)	29.29	30.49	23.49
Angle of Repose (°)	22.39	35.83	36.49

The particle size analysis data indicate that a larger portion of the blend consisted of fines (approximately 45% <150µm), in comparison to roller compacted PVP VA/Soluplus formulations (approximately 35% <150µm), which generated harder ribbons.

The physical properties of the blend pre and post roller compaction was also determined and indicated that by using a dry granulation approach, the flowability may not be significantly improved (**Table 5**). The data also indicate that that by formation of softer ribbons, the powder flow properties may not be improved in comparison to granules formed from harder ribbons (**Table 5**).

In comparison to a direct compression approach, a higher compression force of 8000lbs may be required to achieve the desired tablet hardness, for the dry granulation formulation. However, this may be lower in comparison to 10000lbs compression force that may be required for manufacture of tablets from the granules prepared from harder ribbons.

Table 6: Tablet compression data for 100mg VS-6063 tablet formulations.

Test	PVP VA/Soluplus Dry granulation softer ribbons	PVP VA/Soluplus Dry granulation harder ribbons	PVP VA/Soluplus Direct Compression
Average Hardness (kP)	10.6 %RSD 2.7 Min 10.4 Max 10.8	11.7 %RSD 8.8 Min 10.4 Max 12.7	11.2
Average Tablet Weight (mg)	799.8 %RSD 1.2 Min 779.1 Max 811.0	793.0 %RSD 2.1 Min 763.9 Max 810.2	797.1 %RSD 0.5 Min 791.2 Max 803.2
Average Tablet Thickness (mm)	5.4 %RSD 0.2 Min 5.4 Max 5.4	5.4 %RSD 1.7 Min 5.2 Max 5.5	5.6 %RSD 0.4 Min 5.6 Max 5.6
Compression Force (lbs)	8000	10000	3500
Disintegration time	13	20	8

(mins)			

To determine whether addition of further Crospovidone to the formulation would improve the disintegration time, the Crospovidone content was further increased to a total disintegrant content of 13%, where 3% was added to the extragranular blend. Tablets were compressed using 18.97 x 10.41mm oval tooling tablet tooling on the Carver tablet press. Compression force was adjusted to achieve a tablet hardness of 10 – 14kP. Tablet compression data is shown in **Table 6**.

Table 7: Tablet compression data for 100mg VS-6063 tablet formulations.

Test	Provisional Acceptance Criteria	PVP VA/Soluplus Dry granulation with addition of 3% disintegrant
Average Hardness (kP)	10-14kP	11.6 %RSD 6.9 Min 10.8 Max 12.5
Average Tablet Weight (mg)	Target ± 5.0%, RSD ≤2%	800.2 %RSD 2.2 Min 779.2 Max 835.4
Average Tablet Thickness (mm)	Run and record	5.5 %RSD 2.0 Min 5.4 Max 5.7
Compression Force (lbs)	In-process control, not part of the finished product specification	8000
Disintegration time (mins)	Run and record	10.5

Compared with direct compression, granules made by dry granulation may not improve compressibility or powder flow. While using softer ribbons may improve the disintegration time for the resultant tablets, the dissolution profile was not improved in comparison to the reference product (**Figure 2**), indicating that the functionality of the precipitation inhibitors in the PVP VA/Soluplus formulation may be lost during dry granulation.

Example 3. Dry Granulation of VS-6063 formulations

One batch of the VS-6063 IR formulations has been prepared (**Table 8**), using a dry granulation approach:

Table 8: Composition of 100mg VS-6063 IR tablet formulation

Composition	% w/w	mg/tablet	g/per 300g batch
Intragranular blend			
VS-6063*	13.529	108.23	40.587

(free base)		(100.00)	
HPMC AS-HF	40.586	324.69	121.758
Avicel PH 102	20.943	167.54	62.829
Lactose Monohydrate (FastFlo 316)	20.943	167.54	62.829
Sodium starch glycolate	3.000	24.00	9.000
Magnesium Stearate	0.500	4.00	1.500
Sub-total	**99.501**	**796.00**	**298.503**
Extragranular blend			
Magnesium stearate	0.500	4.00	Final blend for tableting based on yield of granulate available
Total	**100.00**	**800.00**	

The intragranular blend preparation was conducted by screening VS-6063 and all excipients through 600µm sieves before use. The required amount of the functional excipients and the API (*e.g.*, VS-6063) was weighed out and pre-blended for 1 minute using a large plastic spatula, followed by mixing on the Turbula mixer at a setting of 32rpm for 5 minutes. The remaining screened components (except the magnesium stearate) were added to the pre-blend, mixed for 1 minute using a large plastic spatula, followed by mixing on the Turbula mixer at a setting of 32rpm for 15 minutes. Final blending on the Turbula mixer was conducted at a setting of 32rpm for 3 minutes after addition of magnesium stearate. The intragranular blend was then roller compacted.

The granule properties for the IR tablet formulations are shown in **Table 9** and compared to the direct compression batch of the same composition:

Table 9: Powder characterisation for 100mg VS-6063 tablet formulations

Test	HPMC-AS Dry granulation batch 1	HPMC-AS Dry granulation batch 2	HPMC-AS Dry granulation batch 3	HPMC-AS Direct Compression
Bulk Density (g/mL)	Not tested	0.470	0.522	0.282
Tapped Density (g/mL)	Not tested	0.640	0.679	0.570
Hausner Ratio	Not tested	1.36	1.30	2.02

Test	HPMC-AS Dry granulation batch 1	HPMC-AS Dry granulation batch 2	HPMC-AS Dry granulation batch 3	HPMC-AS Direct Compression
Carr's Index (%)	Not tested	26.56	23.20	50.60
Angle of Repose (°)	Not tested	29.87	17.54	38.37

The particle size analysis data indicated a bi-modal particle size distribution for both batches.

The physical properties of the blends were determined and compared to the direct compression formulation (HPMC-AS formulation only). The data indicated that by using a dry granulation approach the flowability may be improved (**Table 9**). However, the Hausner ratio for these experiments was >1.3 and the Carr's index was >**23**%, indicating possibly poor powder flow, cohesiveness and high interparticulate friction. Still the data for angle of repose indicates a passable powder flow.

For both dry granulation formulations in comparison to a direct compression approach, a higher compression force may be required to achieve the desired tablet hardness.

Table 10: Tablet compression data for 100mg VS-6063 tablet formulations.

Test	HPMC-AS Dry granulation batch 1	HPMC-AS Dry granulation batch 2	HPMC-AS Dry granulation batch 3	HPMC-AS Direct Compression
Average Hardness (kP)	12.0 %RSD 7.0 Min 10.6 Max 13.6	12.3 %RSD 3.3 Min 11.9 Max 12.8	12.7 %RSD 8.7 Min 11.9 Max 14.0	13.3 %RSD 3.8 Min 12.8 Max 14.1
Average Tablet Weight (mg)	799.9 %RSD 0.8 Min 780.4 Max 812.2	802.4 %RSD 0.6 Min 787.6 Max 812.9	805.4 %RSD 0.9 Min 797.8 Max 821.6	804.7 %RSD 0.7 Min 796.7 Max 814.4
Average Tablet Thickness (mm)	5.9 %RSD 0.9 Min 5.7 Max 6.0	5.7 %RSD 0.7 Min 5.6 Max 5.8	5.6 %RSD 0.3 Min 5.5 Max 5.6	6.2 %RSD 0.6 Min 6.2 Max 6.3
Compression Force (lbs)	1300	1500	1800	800
Disintegration time (mins)	Not measured	Not measured	10.5	8*

The data from **Figure 3** suggests that for the HPMC-AS formulation by introducing a dry granulation approach, the dissolution profiles of all the batches after the pH switch are comparable to tablets prepared using a direct compression approach.

Example 4. In Vivo Assessment of the Pharmacokinetics of VS-6063 in Various Formulations

Abbreviations used:

Relative bioavailability = AUC_{inf} test formulation/AUC_{inf} reference formulation

C_{max} Maximum concentration observed

T_{max} Time of maximum concentration

$t_{1/2}$ Terminal half life

AUC_{inf} Area under the concentration-time curve from time zero extrapolated to infinity

AUC_{last} Area under the concentration-time curve from time zero to the last quantifiable concentration

Study Design

4 groups of 1 male beagle dog per group received an oral gavage dose of VS-6063 in various formulations in a 4-session crossover design with a minimum 3-day washout period between dose sessions. In each session, VS-6063, VS-6063-25% SDD in Soluplus/PVP-A, VS-6063-25% physical mixture with Soluplus/PVP-A, and VS-6063-10% SDD in EUDRAGIT L100-55 were administered at a target dose level of 10 mg API/kg. Blood samples (anticoagulant: K_2EDTA) were scheduled for collection from each animal prior to dosing and at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after dosing in each dose session. Blood samples were processed for plasma and the plasma was analyzed for VS-6063 by LC-MS/MS. Plasma concentration-time data for individual animals were analyzed to determine the pharmacokinetic profiles of VS-6063.

4 groups of 1 male beagle dog per group received an oral gavage dose of VS-6063 in various formulations in a 4-session crossover design with a minimum 3-day washout period between dose sessions. In each session, VS-6063-25% physical mixture with Soluplus/PVP-A and VS-6063-25% SDD in Soluplus/PVP-A were administered at a target dose level of 20 mg API/kg and VS-6063-50% physical mixture with Soluplus/PVP-A was administered at target dose levels of 10 and 20 mg API/kg. Blood samples (anticoagulant: K_2EDTA) were scheduled for collection from each animal prior to dosing and at 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after dosing in each dose session. Blood samples were processed for plasma and the plasma was analyzed for VS-6063 by LC-MS/MS. Plasma concentration-time data for individual animals were analyzed to determine the pharmacokinetic profiles of VS-6063.

Dose Formulation

VS-6063 was formulated (0.934 correction factor) at a target concentration of 10 mg API/mL in 0.5% (w/v) Methocel A4M in water with 0.1% (v/v) Tween 80. VS-6063-25% SDD in Soluplus/PVP-A was formulated (0.25 correction factor) at a target concentration of 10 mg API/mL in 0.5% (w/v) Methocel A4M in water. VS-6063-25% physical mixture with Soluplus/PVP-A was formulated (0.25 correction factor) at a target concentration of 10 mg API/mL in 0.5% (w/v) Methocel A4M in water. VS-6063-10% SDD in EUDRAGIT L100-55 was formulated (0.10 correction factor) at a target concentration of 10 mg API/mL in 0.5% (w/v) Methocel A4M in water.

VS-6063-25% physical mixture with Soluplus/PVP-A and VS-6063-25% SDD in Soluplus/PVP-A were formulated (0.25 correction factor) at a target concentration of 10 mg API/mL in 0.5% (w/v) Methocel A4M in water. VS-6063-50% Physical mixture with Soluplus/PVP-A was formulated (0.50 correction factor) at target concentrations of 5 mg API/mL and 10 mg API/mL in 0.5% (w/v) Methocel A4M in water.

Dose Administration

4 groups of 1 male beagle dog per group received an oral gavage dose of VS-6063 in various formulations in a 4-session crossover design with a minimum 3-day washout period between dose sessions. In each session, VS-6063, VS-6063-25% SDD in Soluplus/PVP-A, VS-6063-25% physical mixture with Soluplus/PVP-A and VS-6063-10% SDD in EUDRAGIT L100-55 were administered at a target dose level of 10 mg API/kg. Animals were fasted overnight prior to dose administration; water was not withheld. Food was returned at 4 hours post-dose.

Prior to dosing, the body weight of each animal was recorded. Doses (rounded to the nearest 0.01 mL) were calculated based on the pretreatment body weight (kg) and a dose volume of 1 mL/kg. Following the oral gavage dose, the gavage tube was flushed with 10 to 20 mL of water prior to removal of the tube. Dosing syringes were weighed immediately prior to and immediately after dosing each animal, and the quantity of formulation administered to each animal was determined from the difference in syringe weights.

4 groups of 1 male beagle dog per group received an oral gavage dose of VS-6063 in various formulations in a 4-session crossover design with a minimum 3-day washout period between dose sessions. In each session, VS-6063-25% physical mixture with Soluplus/PVP-A and VS-6063-25% SDD in Soluplus/PVP-A were administered at a target dose level of 20 mg API/kg and VS-6063-50% physical mixture with Soluplus/PVP-A was administered at target dose levels of 10 and 20 mg API/kg. Animals

were fasted overnight prior to dose administration; water was not withheld. Food was returned at 4 hours post-dose.

Prior to dosing, the body weight of each animal was recorded. Doses (rounded to the nearest 0.01 mL) were calculated based on the pretreatment body weight (kg) and a dose volume of 2 mL/kg. Following the oral gavage dose, the gavage tube was flushed with 10 to 20 mL of water prior to removal of the tube. Dosing syringes were weighed immediately prior to and immediately after dosing each animal, and the quantity of formulation administered to each animal was determined from the difference in syringe weights.

VS-6063 Concentrations in Plasma

Mean (n=4) plasma concentration-time profiles are shown in **Figure 5** (rectilinear scale).

Following a single oral dose of VS-6063 at a target dose of 10 mg/kg over 4 sessions, plasma concentrations rose at a fairly rapid rate and maximum concentrations for individual animals were reached within 2 to 4 hours post-dose (mean 2.50 hours). Mean concentrations then declined in an apparent first-order manner. Concentrations of VS-6063 were quantifiable in all animals through the 24 hours post-dose (the final time point).

Following a single oral dose of VS-6063-25% SDD in Soluplus/PVP-A, VS-6063-25% physical mixture with Soluplus/PVP-A, and VS-6063-10% SDD in EUDRAGIT L100-55 at a target dose of 10 mg API/kg over 4 sessions, plasma concentrations rose at a fairly rapid rate and maximum concentrations for individual animals were reached within 0.5 to 4 hours post-dose (mean range of 1.75 to 1.88 hours). Mean concentrations then declined in an apparent first-order manner. Concentrations of VS-6063 were quantifiable in all animals through the 24 hours post-dose (the final time point).

Plasma Pharmacokinetics for VS-6063

Plasma pharmacokinetic parameters for VS-6063 are shown in **Tables 13 and 14** .

For VS-6063 at a target dose of 10 mg/kg over 4 sessions, the mean estimated half life was approximately 3.9 hours. Mean C_{max} and mean T_{max} were 614 ng/mL and 2.50 hours, respectively. Mean AUC_{last} was 3100 ng*hr/mL and mean AUC_{inf} was 3120 ng*hr/mL. (**Table 17**)

For VS-6063-25% SDD in Soluplus/PVP-A at a target dose of 10 mg API/kg over 4 sessions, the mean estimated half life was approximately 3.2 hours. Mean C_{max} and mean T_{max} were 1770 ng/mL and 1.75 hours, respectively. Mean AUC_{last} was 8130 ng*hr/mL and mean AUC_{inf} was 8170 ng*hr/mL. (**Table 18**)

For VS-6063-25% physical mixture with Soluplus/PVP-A at a target dose of 10 mg API/kg over 4 sessions, the mean estimated half life was approximately 3.7 hours. Mean C_{max} and mean T_{max} were 1460 ng/mL and 1.75 hours, respectively. Mean AUC_{last} was 7320 ng*hr/mL and mean AUC_{inf} was 7410 ng*hr/mL. (**Table 19**)

For VS-6063-10% SDD in EUDRAGIT L100-55 at a target dose of 10 mg API/kg over 4 sessions, the mean estimated half life was approximately 2.9 hours. Mean C_{max} and mean T_{max} were 1800 ng/mL and 1.88 hours, respectively. Mean AUC_{last} was 8720 ng*hr/mL and mean AUC_{inf} was 8740 ng*hr/mL. (**Table 20**)

Mean pharmacokinetic data suggests relative bioavailability was increased when comparing test formulations (VS-6063-25% SDD, VS-6063-25% physical mixture and VS-6063-10% SDD to the reference formulation (VS-6063), although variability among animals was significant. Mean relative bioavailability estimates were 2.97 (CV 72.7%) for VS-6063-25% physical mixture, 3.21 (CV 43.3%) for VS-6063-10% SDD, and 3.78 (CV 89.9%) for VS-6063-25% SDD. When comparing crossover data; Animal No. 4001 had the lowest exposure to the reference formulation (VS-6063) which contributed to overall variability among animals receiving the treatment (CV 52.8% for mean AUC_{inf}) as well as contributing to the highest relative bioavailability among test formulations.

Although emesis was observed in three of the four subjects dosed with VS-6063-25% physical mixture, mean relative bioavailability was similar to the other test formulations when compared to the reference formulation.

VS-6063 Concentrations in Plasma

Mean plasma concentration-time profiles are shown in **Figure 6** (rectilinear scale).

Following a single oral dose of VS-6063-25% physical mix at a target dose of 20 mg API/kg over 4 sessions, plasma concentrations rose at a rapid rate and maximum concentrations were reached within 0.25 to 1 hour post-dose (mean 0.688 hr). Mean concentrations then declined in an apparent first-order manner. Concentrations of VS-6063 were quantifiable in all animals through the 24 hours post-dose (the final time point).

Following a single oral dose of VS-6063-25% SDD at a target dose of 20 mg API/kg over 4 sessions, plasma concentrations rose at a fairly rapid rate and maximum concentrations were reached within 0.25 to 2 hours post-dose (mean 1.31 hr). Mean concentrations then declined in an apparent first-order manner. Concentrations of VS-6063 were quantifiable in all animals through the 24 hours post-dose (the final time point).

Following a single oral dose of VS-6063-50% physical mixture at target doses of 10 mg API/kg and 20 mg API/kg over 4 sessions, plasma concentrations rose at a fairly rapid rate and maximum concentrations were reached within 0.5 to 2 hours post-dose (mean 1.38 hr) for the 10 mg API/kg dose and within 0.5 to 4 hours post-dose (mean 2.13 hr) for the 20 mg API/kg dose. Mean concentrations then declined in an apparent first-order manner. Concentrations of VS-6063 were quantifiable in all animals through the 24 hours post-dose (the final time point).

Plasma Pharmacokinetics for VS-6063

Plasma pharmacokinetic parameters for VS-6063 are shown in **Tables 15 and 16** .

For VS-6063-25% physical mixture with Soluplus/PVP-A at a target dose of 20 mg API/kg over 4 sessions, the mean estimated half life was approximately 3.0 hours. Mean C_{max} and mean T_{max} were 1670 ng/mL and 0.688 hours, respectively. Mean AUC_{last} was 8670 ng*hr/mL and mean AUC_{inf} was 8700 ng*hr/mL. (**Table 21**)

For VS-6063-25% SDD in Soluplus/PVP-A at a target dose of 20 mg API/kg over 4 sessions, the mean estimated half life was approximately 3.1 hours. Mean C_{max} and mean T_{max} were 1300 ng/mL and 1.31 hours, respectively. Mean AUC_{last} was 5920 ng*hr/mL and mean AUC_{inf} was 5940 ng*hr/mL. (**Table 22**)

For VS-6063-50% physical mixture with Soluplus/PVP-A at a target dose of 10 mg API/kg over 4 sessions, the mean estimated half life was approximately 3.0 hours. Mean C_{max} and mean T_{max} were 680 ng/mL and 1.38 hours, respectively. Mean AUC_{last} was 3390 ng*hr/mL and mean AUC_{inf} was 3400 ng*hr/mL. (**Table 23**)

For VS-6063-50% physical mixture with Soluplus/PVP-A at a target dose of 20 mg API/kg over 4 sessions, the mean estimated half life was approximately 3.5 hours. Mean C_{max} and mean T_{max} were 1160 ng/mL and 2.13 hours, respectively. Mean AUC_{last} was 6900 ng*hr/mL and mean AUC_{inf} was 6930 ng*hr/mL. (**Table 24**)

Observations of emesis corresponded with lower exposure while in other instances there was no correlation.

Pharmacokinetic data suggests that VS-6063-50% physical mixture at target doses of 10 mg API/kg and 20 mg API/kg are dose proportional: mean dose-normalized AUC_{inf} and C_{max} may be similar.

Comparing data from both studies, VS-6063-25% physical mixture (20 mg API/kg) and VS-6063-25% SDD (20 mg API/kg) were less than dose proportional relative to dose-normalized mean

AUC_{inf} and C_{max} with VS-6063-25% physical mixture (10 mg API/kg) and VS-6063-25% SDD (10 mg API/kg) as summarized below in **Table 11**.

Table 11.

Formulation	Dose Level mg API/kg	Mean C_{max}/Dose	Mean AUC_{inf}/Dose
25% Physical Mixture	20	83.5	440
25% Physical Mixture	10	146	741
25% SDD	20	65.0	297
25% SDD	10	177	817

Mean pharmacokinetic data suggests relative bioavailability is similar when comparing test formulations VS-6063-50% physical mixture at target doses of 10 mg API/kg and 20 mg API/kg to reference formulation VS-6063 (10 mg/kg).

Table 12.

Formulation	Dose Level mg API/kg	Mean AUC_{inf}/Dose	Relative Bioavailability
VS-6063 (neat)	10	312	NA
50% Physical Mixture	10	340	1.09
50% Physical Mixture	20	347	1.11

Conclusions

Mean pharmacokinetic data suggests relative bioavailability may be increased when comparing VS-6063-25% SDD in Soluplus (10 mg API/kg), VS-6063-25% physical mixture with Soluplus (10 mg API/kg), and VS-6063-10% SDD in EUDRAGIT L100-55 (10 mg API/kg) to VS-6063 (10 mg/kg), although there was variability among animals. Mean relative bioavailability estimates were 2.97 (CV 72.7%) for VS-6063-25% physical mixture, 3.21 (CV 43.3%) for VS-6063-10% SDD, and 3.78 (CV 89.9%) for VS-6063-25% SDD.

Mean pharmacokinetic data suggests that VS-6063-50% physical mixture with Soluplus/PVP-A at target doses of 10 mg API/kg and 20 mg API/kg are dose proportional. Mean dose-normalized mean AUC_{inf} and mean C_{max} may be generally similar.

Comparing data from both studies, VS-6063-25% physical mixture (20 mg API/kg) and VS-6063-25% SDD (20 mg API/kg) are less than dose proportional when comparing dose-normalized mean AUC_{inf} and mean C_{max} with VS-6063-25% physical mixture (10 mg API/kg) and VS-6063-25% SDD (10 mg API/kg). Dose normalized mean pharmacokinetic data suggests relative bioavailability may be similar when comparing VS-6063-50% physical mixture at target doses of 10 mg API/kg and 20 mg API/kg to VS-6063 (10 mg/kg).

Table 13: Oral (Gavage) Dose Administration of VS-6063 in Various Formulations to Male Beagle Dogs

Session No.	Test Article Formulation	Group No.	Animal No.	Animal Weight (kg)	Formulation Admin (g)	Conc[a] (mg/g)	Dose Administered (mg)	Dose Administered (mg/kg)	Protocol Dose (mg/kg)	Dosing Variance (%)
1	VS-6063	1	1001	8.80	7.986	10	79.86	9.075	10	-9.25
	VS-6063-25% SDD in Soluplus/PVP-A	2	2001	10.74	10.577	10	105.8	9.848	10	-1.52
	VS-6063-25% Phys Mix with Soluplus/PVP-A	3	3001	10.34	10.280	10	102.8	9.942	10	-0.58
	VS-6063-10% SDD in EUDRAGIT L100-55	4	4001	9.14	8.688	10	86.88	9.505	10	-4.95
2	VS-6063-10%SDD in EUDRAGIT L100-55	1	1001	9.22	8.872	10	88.72	9.623	10	-3.77
	VS-6063	2	2001	10.46	9.794	10	97.94	9.363	10	-6.37
	VS-6063-25% SDD in Soluplus/PVP-A	3	3001	11.10	10.951	10	109.51	9.866	10	-1.34
	VS-6063-25% Phys Mix with Soluplus/PVP-A	4	4001	9.62	9.516	10	95.16	9.892	10	-1.08
3	VS-6063-25% Phys Mix with Soluplus/PVP-A	1	1001	8.50	8.459	10	84.59	9.952	10	-0.48
	VS-6063-10% SDD in EUDRAGIT L100-55	2	2001	10.58	9.950	10	99.50	9.405	10	-5.95
	VS-6063	3	3001	10.48	10.462	10	104.6	9.983	10	-0.17
	VS-6063-25% SDD in Soluplus/PVP-A	4	4001	9.38	9.280	10	92.80	9.893	10	-1.07
4	VS-6063-25%SDD in Soluplus/PVP-A	1	1001	8.820	8.800	10	88.00	9.977	10	-0.23

	VS-6063-25% Phys Mix with Soluplus/PVP-A	2	2001	10.800	10.692	10	106.9	9.900	10	-1.00
	VS-6063-10% SDD in EUDRAGIT L100-55	3	3001	10.580	10.390	10	103.9	9.820	10	-1.80
	VS-6063	4	4001	9.380	8.864	10	88.64	9.450	10	-5.50

[a] Assumes a density of 1 g/mL.

Table 14. Mean (n=4) Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063 in Various Formulations to Male Beagle Dogs at 10 mg/kg

Formulation		C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	Relative Bioavailability
VS-6063	Mean	614	2.50	3.86	3120	3100	NA
	SD	302	1.00	0.872	1650	1640	NA
	% CV	49.2	40.0	22.6	52.8	53.0	NA
VS-6063-25% SDD in Soluplus/PVP-A	Mean	1770	1.75	3.24	8170	8130	3.78
	SD	791	1.66	0.501	2490	2480	3.40
	% CV	44.8	94.8	15.5	30.5	30.5	89.9
VS-6063-25% Phys Mix With Soluplus/PVP-A	Mean	1460	1.75	3.71	7410	7320	2.97
	SD	520	1.66	0.551	3400	3310	2.16
	% CV	35.7	94.8	14.9	45.8	45.2	72.7
VS-6063-10% SDD in EUDRAGIT L100-55	Mean	1800	1.88	2.93	8740	8720	3.21
	SD	495	1.55	0.351	3560	3540	1.39
	% CV	27.6	82.6	12.0	40.7	40.7	43.3

Relative bioavailability = AUC_{inf} test formulation/AUC_{inf} reference formulation

Table 15. Oral (Gavage) Dose Administration of VS-6063 in Various Formulations to Male Beagle Dogs

Session No.	Test Article Formulation	Group No.	Animal No.	Animal Weight (kg)	Formulation Admin (g)	Conc[a] (mg/g)	Dose Administered (mg)	Dose Administered (mg/kg)	Protocol Dose (mg/kg)	Dosing Variance (%)
1	VS-6063-25% Phys Mix with Soluplus/PVP-A	1	1001	9.76	19.44	10	194.35	19.91	20	-0.44
	VS-6063-25% SDD in	2	2001	9.40	18.64	10	186.38	19.83	20	-0.86

	Soluplus/PVP-A									
	VS-6063-50% Phys Mix with Soluplus/PVP-A	3	3001	8.64	17.01	5	85.03	9.84	10	-1.59
	VS-6063-50% Phys Mix with Soluplus/PVP-A	4	4001	9.68	19.26	10	192.58	19.89	20	-0.53
2	VS-6063-50% Phys Mix with Soluplus/PVP-A	1	1001	10.08	19.98	10	199.75	19.82	20	-0.92
	VS-6063-25% Phys Mix with Soluplus/PVP-A	2	2001	9.08	18.33	10	183.25	20.18	20	0.91
	VS-6063-25% SDD in Soluplus/PVP-A	3	3001	9.00	17.95	10	179.52	19.95	20	-0.27
	VS-6063-50% Phys Mix with Soluplus/PVP-A	4	4001	9.90	19.49	5	97.44	9.84	10	-1.58
3	VS-6063-50% Phys Mix with Soluplus/PVP-A	1	1001	9.94	19.45	5	97.24	9.78	10	-2.18
	VS-6063-50% Phys Mix with Soluplus/PVP-A	2	2001	8.68	17.08	10	170.83	19.68	20	-1.60
	VS-6063-25% PHYS mix with Soluplus/PVP-A	3	3001	8.40	16.61	10	166.10	19.77	20	-1.13
	VS-6063-25% SDD in Soluplus/PVP-A	4	4001	9.80	18.96	10	189.62	19.35	20	-3.26
4	VS-6063-25% SDD in Soluplus/PVP-A	1	1001	10.50	20.45	10	204.49	19.48	20	-2.62
	VS-6063-50% Phys Mix with Soluplus/PVP-A	2	2001	9.00	17.70	5	88.48	9.83	10	-1.69
	VS-6063-50% Phys Mix with Soluplus/PVP-A	3	3001	8.92	17.65	10	176.47	19.78	20	-1.08
	VS-6063-25% Phys Mix with Soluplus/PVP-A	4	4001	10.40	20.61	10	206.05	19.81	20	-0.94

[a] Assumes a density of 1 g/mL.

Table 16 Mean (n=4) Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063 in Various Formulations to Male Beagle Dogs at 10 or 20 mg API/kg

Formulation Dose		C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max}/Dose	AUC_{inf}/Dose
VS-6063-25% Phys Mix with Soluplus/PVP-A	Mean	1670	0.688	3.01	8700	8670	83.5	440
20 mg API/kg	SD	580	0.375	0.156	3400	3390	29.0	170

	% CV	34.7	54.5	5.2	39.1	39.1	34.7	39.1
VS-6063-25% SDD in Soluplus/PVP-A	Mean	1300	1.31	3.12	5940	5920	64.9	297
20 mg API/kg	SD	672	0.851	0.289	1640	1640	33.6	82.1
	% CV	51.8	64.8	9.3	27.6	27.7	51.8	27.6
VS-6063-50% Phys Mix with Soluplus/PVP-A	Mean	680	1.38	3.00	3400	3390	68.0	340
10 mg API/kg	SD	190	0.750	0.0208	1150	1150	19.0	115
	% CV	28.0	54.5	0.700	33.9	33.8	28.0	33.9
VS-6063-50% Phys Mix with Soluplus/PVP-A	Mean	1160	2.13	3.51	6930	6900	57.9	347
20 mg API/kg	SD	516	1.44	0.813	3500	3500	25.8	175
	% CV	44.6	67.6	23.1	50.5	50.8	44.6	50.5

Table 17 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063 to Male Beagle Dogs at 10 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)
1	1001	537	2	3.49	2830	2820
2	2001	987	4	3.42	5200	5180
3	3001	671	2	3.39	3240	3230
4	4001	260	2	5.17	1200	1180
	Mean	614	2.50	3.86	3120	3100
	SD	302	1.00	0.872	1650	1640
	% CV	49.2	40.0	22.6	52.8	53.0

Table 18 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-25% SDD in Soluplus/PVP-A to Male Beagle Dogs at 10 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	Relative Bioavailability
4	1001	2390	0.5	3.58	9880	9840	3.49
1	2001	1280	4	2.58	7460	7450	1.43
2	3001	912	2	3.12	4950	4930	1.53
3	4001	2490	0.5	3.67	10400	10300	8.68

	Mean	1770	1.75	3.24	8170	8130	3.78
	SD	791	1.66	0.501	2490	2480	3.40
	% CV	44.8	94.8	15.5	30.5	30.5	89.9

Table 19 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-25% Physical Mixture With Soluplus/PVP-A to Male Beagle Dogs at 10 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	Relative Bioavailability
3	1001[a]	1810	0.5	3.26	6420	6350	2.27
4	2001	1750	4	4.40	12000	11800	2.31
1	3001	691	2	3.92	3890	3850	1.20
2	4001	1580	0.5	3.27	7320	7300	6.12
	Mean	1460	1.75	3.71	7410	7320	2.97
	SD	520	1.66	0.551	3400	3310	2.16
	% CV	35.7	94.8	14.9	45.8	45.2	72.7

[a] Regression R square value <0.9

Table 20 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-10% SDD in EUDRAGIT L100-55 to Male Beagle Dogs at 10 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	Relative Bioavailability
2	1001	2180	4	2.77	11400	11400	4.03
3	2001	2200	1	3.33	12200	12100	2.35
4	3001	1160	2	3.10	5700	5680	1.76
1	4001	1650	0.5	2.53	5640	5640	4.72
	Mean	1800	1.88	2.93	8740	8720	3.21
	SD	495	1.55	0.351	3560	3540	1.39
	% CV	27.6	82.6	12.0	40.7	40.7	43.3

Table 21 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-25% Physical Mixture With Soluplus/PVP-A to Male Beagle Dogs at 20 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max}/Dose	AUC_{inf}/Dose
1	1001	952	1	3.15	4770	4750	47.6	240

2	2001	1570	1	3.13	7200	7180	78.5	360
3	3001	1810	0.5	2.87	10300	10300	90.5	520
4	4001	2350	0.25	2.87	12500	12500	120	630
	Mean	1670	0.688	3.01	8700	8670	83.5	440
	SD	580	0.375	0.156	3400	3390	29.0	170
	% CV	34.7	54.5	5.2	39.1	39.1	34.7	39.1

Table 22 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-25% SDD in Soluplus/PVP-A to Male Beagle Dogs at 20 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max}/Dose	AUC_{inf}/Dose
4	1001	2240	0.25	2.73	7870	7860	112	394
1	2001	650	2	3.15	3930	3920	32.5	197
2	3001	1200	2	3.43	6380	6350	60.0	319
3	4001	1100	1	3.18	5580	5560	55.0	279
	Mean	1300	1.31	3.12	5940	5920	64.9	297
	SD	672	0.851	0.289	1640	1640	33.6	82.1
	% CV	51.8	64.8	9.3	27.6	27.7	51.8	27.6

Table 23 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-50% Physical Mixture With Soluplus/PVP-A to Male Beagle Dogs at 10 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max}/Dose	AUC_{inf}/Dose
3	1001	809	2	3.03	3970	3960	80.9	397
4	2001	398	0.5	3.01	1820	1810	39.8	181
1	3001	733	2	2.98	3350	3340	73.3	335
2	4001	778	1	3.00	4470	4450	77.8	447
	Mean	680	1.38	3.00	3400	3390	68.0	340
	SD	190	0.750	0.0208	1150	1150	19.0	115
	% CV	28.0	54.5	0.700	33.9	33.8	28.0	33.9

Table 24 Plasma Pharmacokinetic Parameters for VS-6063 Following an Oral Gavage Dose of VS-6063-50% Physical Mixture With Soluplus/PVP-A to Male Beagle Dogs at 20 mg API/kg

Session	Animal Number	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	AUC_{inf} (hr*ng/mL)	AUC_{last} (hr*ng/mL)	C_{max}/Dose	AUC_{inf}/Dose
2	1001	1210	0.5	3.32	6250	6230	60.5	312

3	2001	1710	2	2.88	11000	10900	85.5	549
4	3001	1250	2	3.14	7930	7900	62.5	396
1	4001	462	4	4.70	2570	2530	23.1	129
	Mean	1160	2.13	3.51	6930	6900	57.9	347
	SD	516	1.44	0.813	3500	3500	25.8	175
	% CV	44.6	67.600	23.100	50.5	50.8	44.6	50.5

Example 5. Clinical Study Protocol: Phase I Study of Safety, Bioavailability, and Pharmacodynamics of Selected Formulations of VS-6063

Study Design

In a Phase I, open-label, single center, single dose, partially randomized trial, the safety, bioavailability, and pharmacodynamics of prototype and reference formulations of VS-6063 were investigated in healthy male subjects.The study was comprised of four periods, each of which adhered to the same study design and involved 24 healthy male subjects between 40 and 65 years of age with a body mass index between 18.0 and 35.0 kg/m^2. Following a 28 day screening period, the subjects were admitted to the clinical unit the morning prior to dosing day (Day -1) and were dosed in the morning of Day 1. Subjects in Regimens A and B were administered VS-6063 following an overnight fast of about 10 hours, while subjects in Regimens C and D were administered VS-6063 within 30 minutes of starting a high fat breakfast, which was consumed within 25 minutes. Subjects remained on site until 36 hours after dosing. There was a minimum washout period of 7 days between the administration of each regimen. A follow-up phone call took place 7 to 10 days post final dose in periods 3 and 4 to ensure the ongoing well-being of the subjects.

Table 25. Summary of pharmacokinetic results

	Regimen A	**Regimen B**	**Regimen C**	**Regimen D**
Formulation **Dose** **Fasted/Fed** **Parameter**	**Reference** **200 mg** **Fasted** **N = 24**	**Prototype** **100 mg** **Fasted** **N = 24**	**Prototype** **100 mg** **Fed** **N = 23**	**Reference** **200 mg** **Fed** **N = 9**
T_{lag}[a] (h)	0.000 (0.00–0.00)	0.042 (0.00–0.50)	0.000 (0.00–0.52)	0.000 (0.00–1.00)
T_{max}[a] (h)	1.000 (0.50–3.00)	2.000 (1.00–4.00)	4.000 (2.00–10.02)	4.000 (2.00–6.00)

C_{max} (ng/mL)	212 (72.8%)	446 (32.3%)	262 (43.5%)	427 (66.7%)
C_{12} (ng/mL)	6.1 (78.0%)	15.1 (88.8%)	22.7 (80.6%)	38.5 (174.0%)
C_{24} (ng/mL)	3.30 (59.9%) [n = 23]	3.72 (63.4%)	4.45 (74.2%)	4.52 (93.2%)
AUC_{last} (ng.h/mL)	883 (69.2%)	1910 (36.6%)	1590 (44.6%)	2490 (75.8%)
AUC_{inf} (ng.h/mL)	755 (46.0%) [n = 2]	2350 (29.2%) [n = 11]	1790 (37.0%) [n = 12]	2970 (75.4%) [n = 7]
$AUC_{\%extrap}$ (%)	1.581 (155.7%) [n = 2]	1.028 (41.8%) [n = 11]	1.232 (46.1%) [n = 12]	0.574 (69.3%) [n = 7]
lambda-z	0.16125 (214.7) [n = 2]	0.10403 (31.4%) [n = 11]	0.09156 (21.4%) [n = 12]	0.13372 (40.1%) [n = 7]
$\alpha\ t_{1/2}$ (h) (Distributional Component)	1.880 (18.9%)	1.989 (20.1%)	2.082 (21.4%)	2.154 (15.9%)
$t_{1/2}$ (h)	4.299 (214.7%) [n = 2]	6.663 (31.4%) [n = 11]	7.571 (21.4%) [n = 12]	5.183 (40.1%) [n = 7]

[a] Median (range)

Abbreviations: T_{lag}[a]: the elapsed time from dosing at which VS-6063 was first quantifiable in a concentration vs time profile; C_{max}: the maximum observed VS-6063 concentration; T_{max}[a]: the time from dosing at which C_{max} was present; C_{12}: the observed VS-6063 concentration at 12 h; C_{24}: the observed VS-6063 concentration at 24 h; AUC_{last}: the area under the concentration vs time curve from time zero to the time of the last quantifiable concentration; AUC_{inf}: the area under the concentration vs time curve from time zero extrapolated to infinity; $AUC_{\%extrap}$: the percentage of $AUC_{(0\text{-}inf)}$ accounted for by extrapolation; lambda-z: slope of the regression time passing through the apparent elimination phase in a concentration vs time plot; $t_{1/2}$: the apparent elimination half-life; $\alpha\ t_{1/2}$: the distributional half-life of VS-6063 occurring over the time range between C_{max} and approximately 12 h post-dose.

Statistical Methods

Formal statistical analysis was performed on the dose corrected pharmacokinetic (PK) parameters AUC_{last}, AUC_{inf}, and C_{max} to assess relative bioavailability and the presence of food effects. The PK

parameters were subjected to a natural logarithmic transformation and were analyzed using mixed model techniques. Adjusted geometric mean rations (GMRs) and 90% confidence intervals (CIs) for the adjusted GMRs were calculated for the comparisons of the different regimens. The CIs were based on the t-distribution and the variances estimated by the model using the Kenward-Roger method for calculating the degrees of freedom.

Study Results

Following administration of either a 200 mg VS-6063 reference formulation tablet (comprising VS-6063, microcrystalline cellulose PH 102, Fastflo 316, sodium starch glycolate, and magnesium stearate) or a 100 mg VS-6063 prototype formulation tablet (comprising VS-6063, HPMCAS-HF, microcrystalline cellulose PH 102, Fastflo 316, sodium starch glycolate, and magnesium stearate) in the fed and fasted states, plasma concentrations rose to a maximal level immediately following dosing. This was followed by a biphasic reduction in plasma levels over the 24 h sampling period, as VS-6063 was distributed and eliminated from the systemic circulation. No real difference in half-life could be determined between the reference and prototype formulations in either the fed or fasted states.

In the fasted state, the 100 mg prototype formulation administered in Regimen B lead to significantly higher exposure in comparison to the 200 mg reference formulation in Regimen A. The adjusted GMRs and 90% CIs for Regimen B/Regimen A based on C_{max} and AUC_{last} were 421.33 (348.4%, 509.5%) and 433.05 (366.8%, 511.3%), respectively, equating to a 4-fold increase in exposure as a result of the change in formulation. In addition to the increase in bioavailability, there was evidence of a decrease in variability observed upon administration of the prototype formulation associated with exposure parameters from approximately 70% to 30%.

Comparison of the time taken to reach maximum plasma concentrations of VS-6063 was 2 to 4 times longer in the fed state than in the fasted state (as assessed by C_{max} and AUC_{last}), indicating a food effect on the rate of absorption. In addition, determination of exposure following administration of the 200 mg VS-6063 reference formulation in both the fed and fasted state indicate a higher level of exposure in the fed state relative to the fasted state, which signifies the presence of a food effect for the reference formulation. Despite these effects, an increase in VS-6063 exposure was still observed when the prototype formulation was administered compared with the reference formulation in the fed state. The adjusted GMRs and 90% CIs for Regimen C/Regimen D based on C_{max} and AUC_{last} were 129.8 and 125.1, respectively.

Overall, the maximum exposure was achieved with the prototype formulation administered in the fasted state. Equivalent exposure in terms of AUC_{inf} was also achieved with the prototype formulation in the fed state.

VS-6063 was well tolerated when administered in both the fed and fasted states in both the reference and prototype formulations. There were no serious adverse events (AEs) or severe AEs reported during the study, and no subject was withdrawn as a result of an AE. The overall incidence of total AEs was low, with 12 AEs reported by 9 subjects. The incidence of AEs was highest for Regimen C (5 subjects) compared to Regimens A, B, and D (3 subjects, 2 subjects, and 1 subject, respectively). The most common AE was headache, which was reported by 3 subjects. All other AEs were reported by 1 subject. No subject reported an AE that was related to VS-6063, and nearly all AEs were mild in severity. There were no clinically significant findings in any laboratory assessments, measurement of vital signs, ECGs, or physical examinations.

CLAIMS

1. A pharmaceutical composition comprising VS-6063, or a pharmaceutically acceptable salt thereof, admixed with polyvinylpyrrolidone vinyl acetate copolymer (PVP VA) and a copolymer comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate, wherein the composition is configured in an oral dosage form.

2. The pharmaceutical composition of claim 1, wherein the oral dosage form comprises 5 to 50%, 5 to 30%, 10 to 30%, 10 to 20%, 12 to 15%, or 13% of VS-6063, or a pharmaceutically acceptable salt thereof, per weight of the oral dosage form.

3. The pharmaceutical composition of claim 1, wherein the VS-6063, or a pharmaceutically acceptable salt thereof, is present at 13% per weight of the oral dosage form.

4. The pharmaceutical composition of claim 1, wherein the oral dosage form is a tablet.

5. The pharmaceutical composition of claim 4, wherein the tablet is provided by direct compression of a physical blend or mixture.

6. The pharmaceutical composition of claim 5, wherein the physical blend or mixture is provided by a dry granulation process.

7. The pharmaceutical composition of claim 1, further comprising a disintegrant.

8. The pharmaceutical composition of claim 7, wherein the disintegrant is crosslinked polyvinylpyrrolidone or crospovidone, carboxymethyl cellulose or croscarmellose sodium, or a modified starch.

9. The pharmaceutical composition of claim 7, wherein the disintegrant is a polyvinylpolypyrrolidone.

10. The pharmaceutical composition of claim 7, wherein the disintegrant is present at 0 to 30%, 5 to 25%, 5 to 20%, 5 to 15%, or 10% per weight of the oral dosage form.

11. The pharmaceutical composition of claim 1, further comprising a lubricant.

12. The pharmaceutical composition of claim 11, wherein the lubricant is talc, silica, or fats, optionally wherein the lubricant is magnesium stearate, optionally wherein the lubricant is present at 0.1 to 2%, 0.2 to 1.5%, 1%, or 0.5% per weight of the oral dosage form.

13. The pharmaceutical composition of claim 1, further comprising one or more fillers.

14. The pharmaceutical composition of claim 13, wherein the filler is a polyol.

15. The pharmaceutical composition of claim 14, wherein the polyol is mannitol-starch, mannitol, or sorbitol.

16. The pharmaceutical composition of claim 1, wherein the composition comprises VS-6063 free base or VS-6063 hydrochloride.

17. An oral dosage form comprising:

VS-6063, or a pharmaceutically acceptable salt thereof, in an amount from 10 to 15% by weight on a dry weight basis,

a first pharmaceutically acceptable excipient in an amount from 15 to 25% by weight on a dry weight basis, wherein the first pharmaceutically acceptable excipient is polyvinyl pyrrolidone vinyl acetate copolymer (PVP VA),

a second pharmaceutically acceptable excipient in an amount from 15 to 25% by weight on a dry weight basis, wherein the second pharmaceutically acceptable excipient is a copolymer comprising polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate,

a pharmaceutically acceptable filler in an amount from 30 to 40% by weight on a dry weight basis,

a pharmaceutically acceptable disintegrant in an amount from 5 to 15% by weight on a dry weight basis, and

a pharmaceutically acceptable lubricant in an amount from 0.2 to 1.5% by weight on a dry weight basis.

18. The oral dosage form of claim 17, wherein the pharmaceutically acceptable filler is mannitol-starch.

19. The oral dosage form of claim 17, wherein the pharmaceutically acceptable disintegrant is crospovidone.

20. The oral dosage form of claim 17, wherein the pharmaceutically acceptable lubricant is magnesium stearate.

COMPOSITIONS AND METHODS FOR TREATMENT OF ABNORMAL CELL GROWTH

Abstract

This invention relates to oral dosage forms and methods that are useful in the treatment of abnormal cell growth, such as cancer, in mammals, especially humans.

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