ECOG-ACRIN cancer research group
Reshaping the future of patient care

Operations Office

July 10, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #21 to EAY131-U, *VS-6063 (defactinib) in Patients with Tumors with NF2 Loss*.

Please replace your current copy of the protocol and Informed Consent document (if ICD changed) with this (these) updated version(s). We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

**IRB Review Requirements:**

**This addendum has been reviewed and approved by the Central IRB which is the sole IRB of record for this study.**

**Implementation of this addendum must occur on the activation date**. Sites are not permitted to conduct the study utilizing outdated versions of any MATCH protocol documents after the activation date of this addendum.]

This addendum is in response to Dr. Charles Kunos June 19, 2019 Request for Amendment for Defactinib.

The following revisions to EAY131-U protocol have been made in this addendum:

| | Section | Change |
|---|---|---|
| 1. | Cover Page | Updated Version date. |
| 2. | 3.3 | Updated the VS-6063 (defactinib hydrochloride) CAEPR list with version 2.3, April 5, 2019. |

The following revisions to EAY131-U Informed Consent Document have been made in this addendum:

| | Section | Change |
|---|---|---|
| 1. | Page 1 | Updated Version Date. |
| 2. | What possible risks can I expect from taking part in this study? | Updated the VS-6063 (defactinib hydrochloride) possible risks risk list with version 2.3 April 5, 2019. |



28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

If you have any questions regarding this addendum, please contact aagu@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-U so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

Enclosure

CC:
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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-U

# Molecular Analysis for Therapy Choice (MATCH)

## MATCH Treatment Subprotocol U: VS-6063 (defactinib) in Patients with Tumors with NF2 Loss


VS-6063 (DEFACTINIB) TREATMENT SUBPROTOCOL CHAIR: David Jackman, MD

VS-6063 (DEFACTINIB) TREATMENT SUBPROTOCOL CO-CHAIR: Marjorie Zauderer, MD



**Version Date:** July 10, 2019
**NCI Update Date:** August 12, 2015


**NOTE: This subprotocol (EAY131-U) should be used in conjunction with the MATCH Master Protocol (EAY131*)***

***SUBPROTOCOL ACTIVATION DATE***

August 12, 2015 (incorporated in Addendum #1)
Update #2 – 8/15
Addendum #2 – 2/16
Addendum #3 – 5/16
Addendum #4 – 7/16
Addendum #5 – 12/16
Addendum #7 – 3/17
Addendum #11 – 8/17
Addendum #21

| Agent | IND# | NSC# | Supply |
|---|---|---|---|
| VS-6063 (defactinib) | IND Sponsor: DCTD, NCI IND#: [redacted] | 781450 | NCI Supplied |

# Table of Contents

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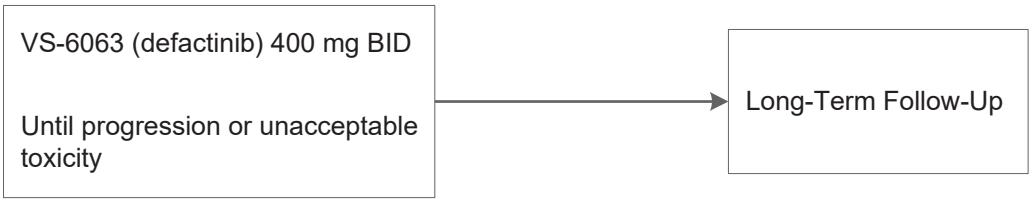
## Schema




Cycle = 28 days
Accrual Goal: 35

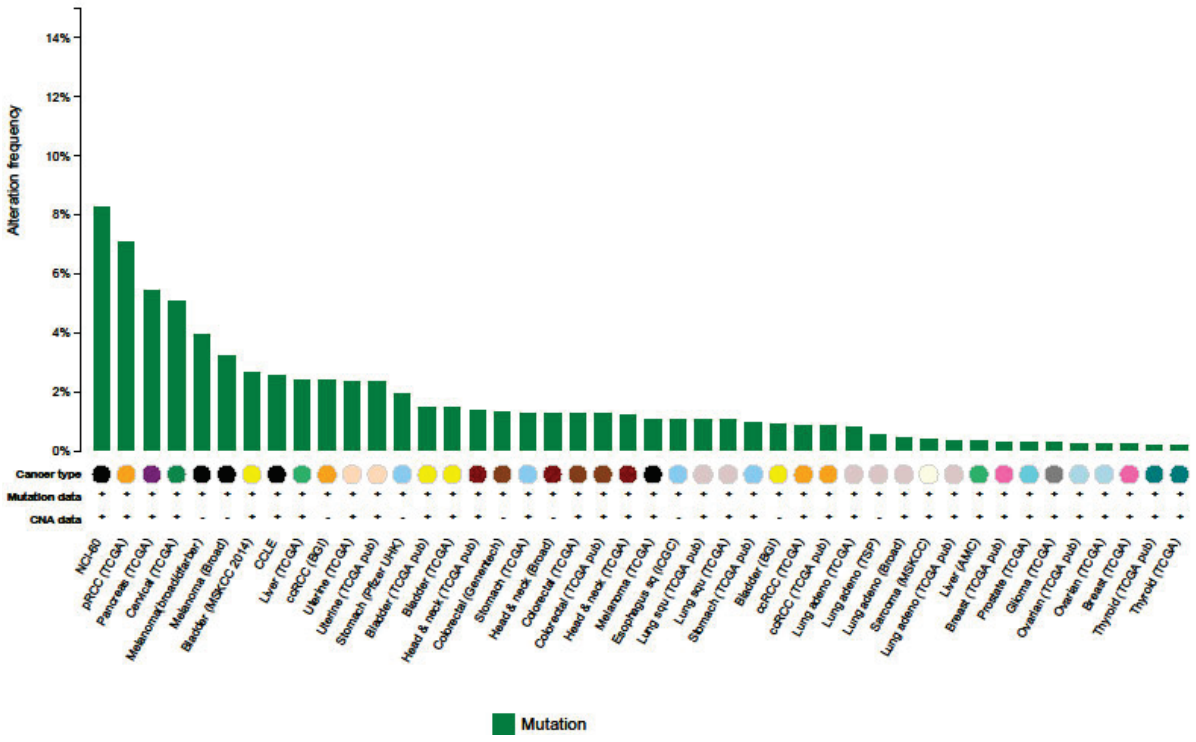
# 1. Introduction

## 1.1 The Potential Role of FAK Inhibition in Human Cancers

High expression of the cytoplasmic protein tyrosine kinase focal adhesion kinase (FAK) has been frequently demonstrated to be associated with invasive and metastatic malignancies, implicating FAK in malignant progression of multiple epithelial tumors.[1] FAK localizes to focal adhesions and mediates physical attachment of cells to the extracellular matrix (ECM), integrating signals from growth factor receptors and integrins. FAK is known to promote tumor cell survival and resistance to anoikis (induction of apoptosis upon loss of contact with the ECM), via the *ADRB2*/Src signaling pathway. The ability to survive without ECM contact is a hallmark of metastatic cells, allowing them to leave the parent tumor and migrate to and colonize distant tissues. This ability is also characteristic of cancer stem cells (CSC) and suggests that FAK modulation may be a new therapeutic target in cancer.

In some malignancies, the neurofibromatosis type 2 gene (*NF2*) may be mutated or otherwise inactivated. *NF2* is a tumor suppressor gene that encodes the protein Merlin (moesin-exrin-radixin-like protein). Bi-allelic inactivation of *NF2* through mutation and/or deletion is known to occur in several malignancies, including mesothelioma, vestibular Schwannomas, and meningiomas, resulting in inactive Merlin. Merlin has been demonstrated to play a role in regulation of the FAK pathway. Increased activation of FAK has been demonstrated in *NF2*-mutated Merlin-negative mesothelioma cells, resulting in increased cell motility, spreading, and invasiveness. Restoration of Merlin expression in these cells both attenuated FAK phosphorylation and decreased invasiveness,[2] indicating that FAK may be an important therapeutic target for diseases in which *NF2* mutations occur.

NF2 mutations have been demonstrated in several tumor types as well as cell lines, as shown in the figure below from cBioPortal:




1.2 VS-6063 (defactinib)

VS-6063 (also known as defactinib, and previously known as PF-04554878) is a small molecule, orally available potent adenosine-5'-triphosphate (ATP)-competitive, reversible inhibitor of FAK and proline-rich tyrosine kinase-2 (Pyk2), each with half maximal inhibitory concentration ($IC_{50}$) < 0.6 nM.

VS-6063 (defactinib) is formulated as a white to off-white oval tablet for oral administration and supplied in single unit dose strength of 200 mg. In addition to VS-6063 (defactinib), formulation components include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and magnesium stearate.

More information is available in the investigator's brochure for VS-6063.

1.3 Non-Clinical Data

1.3.1 Primary Pharmacology

To determine the *in vitro* activity of VS-6063 against mesothelioma cell lines and to test whether low Merlin expression correlates with sensitivity to VS-6063 (defactinib), the mesothelioma tumor microenvironment was modeled using 3-dimentional culture. Mesothelioma cell lines were initially characterized by Western blot analysis for Merlin expression. MSTO-211H, H226 and MM692 cell lines had high levels of Merlin expression, while MM129 and MM690 had no detectable Merlin expression. The Merlin status of the cell lines was found to correlate with sensitivity to VS-6063 (defactinib), with a dramatic bifurcation between the Merlin-negative and Merlin-positive cell lines. Mutant NF2 MPM cells were found to be especially sensitive to the FAK inhibitor VS-6063 (defactinib) with EC50 values

below 800 nM, in contrast to wild-type NF2 MPM cell lines which were less sensitive with EC50 values above 3 μM. Ectopic expression of a non-phosphorylatable artificial mutant of NF2 (NF2-S518A) in NF2-mutant MPM cells abolished the enhanced sensitivity to FAK inhibitors. The reactivation of the FAK pathway with the introduction of a non-phosphorylatable form of NF2 that is resistant to FAK inhibition further supports the potential importance of this pathway and its targeted inhibition.

In addition to its antiproliferative activity against mesothelioma cell lines, VS-6063 (defactinib) may have an effect on cancer stem cells (CSCs). Using multiple cancer stem cell assays, both *in vitro* and *in vivo*, Verastem has observed that FAK inhibitors, including VS-6063 (defactinib), effectively kill CSCs. CSCs are a subset of tumor cells that are both resistant to standard therapies and capable of seeding new tumors, resulting in tumor recurrence and metastasis. This increase in CSCs following standard-of-care treatment is thought to limit the ability of standard cancer drugs to confer durable clinical responses for patients. This hypothesis is supported by *in vitro* experiments with human mesothelioma cell lines, which show that chemotherapeutic agents such as pemetrexed and cisplatin enrich for cells testing positive to the Aldefluor assay (a marker of cancer stem cells). FAK inhibitors, including VS-6063 (defactinib), effectively reduced the proportion of Aldefluor-positive cells, suggesting that targeting FAK might reduce the CSC population and reverse the resistance that develops to standard chemotherapy.

In light of these data, inhibition of FAK by compounds like VS-6063 (defactinib), may represent an important therapeutic approach in appropriate patients. Moreover, given the preferential sensitivity of Merlin-low cell lines to VS-6063 (defactinib), it is additionally hypothesized that VS-6063 (defactinib) may be especially beneficial in those subjects whose tumors have reduced or absent Merlin expression.

[redacted]

[redacted]

1.3.3 Summary of Pharmacokinetics, Metabolism, and Pharmacodynamics

VS-6063 (defactinib) is a potent and selective ATP-competitive, reversible inhibitor of recombinant human FAK and Pyk2 in biochemical and cell-based assays. A comprehensive evaluation of

selectivity against a large panel of other kinases in enzyme assays demonstrated that VS-6063 (defactinib) is highly selective for FAK and Pyk2, strongly suggesting that its predominant pharmacologic activity is mediated by inhibition of FAK and Pyk2.

VS-6063 (defactinib) demonstrated antitumor efficacy in multiple human tumor xenograft models in nude mice including mesothelioma, glioma, ovarian, colon, and pancreatic carcinoma models. In these studies, oral administration of VS-6063 (defactinib) was demonstrated to result in significant growth inhibition or regression of established tumors at well-tolerated dose levels. In addition, studies investigating the dose- and time-dependent inhibition of FAK activity following oral administration of VS-6063 (defactinib) provided insight towards the relationship of inhibition of FAK to antitumor efficacy and the PK/pharmacodynamic relationship for this compound. The PK/pharmacodynamic relationship and subsequent target $C_{eff}$ was determined by measuring VS-6063 (defactinib) in plasma samples isolated from the same individual mice in which target inhibition data was generated.

[redacted]

[redacted]

1.4 Previous Human Experience

The safety and tolerability of VS-6063 (defactinib) have been tested in a first-in-human Phase I study in subjects with solid tumors. A total of 46 subjects received oral doses of VS-6063 (defactinib) ranging from 12.5 to 750 mg BID, 36 subjects in a fasted state and 10 in a fed state. Overall VS-6063 (defactinib) was safe and well tolerated. Exposure did not increase significantly above 425 mg BID; therefore the maximum tolerated dose (MTD) was not established. On the basis of both the Phase I data and the nonclinical pharmacodynamic studies, the recommended Phase 2 dose has been established as 400 mg BID.

1.4.1 Potential Risk

Evidence from *in vitro* and *in vivo* toxicological assessments of VS-6063 (defactinib) and from the Phase I first-in-human (FIH) study suggests VS-6063 (defactinib) has a safety profile supportive of its development as an anticancer therapeutic.

In the Phase I FIH study, VS-6063 (defactinib) was safe and well tolerated. The most frequently reported adverse events (AEs) were from the system organ classes (SOCs) of GI disorder and nervous system disorder. A total of 10 subjects experienced 15 serious AEs (SAEs) during this study. All 15 SAEs were considered not related to the study drug.

Dose-limiting toxicities (DLTs) were observed in 5 subjects; hyperbilirubinemia was considered a DLT for 2 subjects in the fasting cohort (300 mg BID [n=1] and 425 mg BID [n=1]) and 1 subject in the fed cohort (425 mg BID]). Other DLTs observed were headache in the 200 mg BID fasting cohort [n=1] and fatigue in the 425 mg BID fed cohort [n=1].

The most frequently reported treatment-emergent AEs (TEAEs) in the Phase I FIH study were nausea (19 of 46 [41.3%] subjects) followed by fatigue (18 of 46 [39.1%] subjects), vomiting (15 of 46 [32.6%] subjects), and hyperbilirubinemia (15 of 46 [32.6%] subjects). Most AEs were grade 1 or 2 in severity and resolved without sequelae.

1.4.2 Other Potential Risks

1.4.2.1 Hyperbilirubinemia

Includes data up to 28 days after last dose of study drug Highest grade reported for each subject. Overall, 15 subjects (32.6%) reported hyperbilirubinemia. In all these cases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were within normal limits. This unconjugated hyperbilirubinemia was generally asymptomatic and reversible with dosing holiday or continued treatment.

1.4.2.2 Blood Pressure

A total of 9 (19.6%) subjects had a maximum increase from Baseline ≥ 30 mmHg in supine systolic blood pressure (BP), and 9 (19.6%) subjects had a maximum increase from Baseline ≥ 30 mmHg in standing systolic BP. A total of 8 (17.4%) subjects had maximum increase from Baseline ≥ 20 mmHg in supine diastolic BP, and 5 (10.9%) subjects had maximum increase from Baseline ≥ 20 mmHg in standing diastolic BP.

1.4.2.3 Phototoxicity

VS-6063 (defactinib) exhibits an absorbance peak in the range of UV-A/UV-B light, specifically at 290 nm. Clinical studies of other drugs that modulate mitogen-activated protein kinase pathway components have exhibited skin phototoxicity.

Beyond dermatological monitoring, potential risks of direct phototoxicities induced by VS-6063 (defactinib) will be further minimized by advising that subjects minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Subjects will be informed that relevant sun exposure may occur even through glass, such as while driving.

1.4.2.4 Reproductive

On the basis of extrapolations from nonclinical toxicities, potential manifestations in humans may also include impaired fertility. The effect of VS-6063 (defactinib) on a developing fetus is unknown. Therefore, men and women of childbearing potential will be required to agree to use adequate contraception (double barrier birth control or abstain from all sexual activity) for the duration of study therapy and for 3 months after the last dose of VS-6063 (defactinib).

1.4.3 Clinical Efficacy

In the Phase I FIH study in subjects with solid tumors, best response of SD was achieved in 16 of 46 (34.8%) subjects. These responses appeared to be related to dose since SD was not achieved any of the 9 subjects (0/9) who received doses of < 100 mg BID (12.5, 25, and 50 mg in the 9 subjects BID). However, 16 of 37 (43%) subjects who received doses of ≥ 100 mg BID experienced SD as their best response to treatment.

1.4.4 Summary of Clinical Pharmacokinetics

In the previously conducted Phase I clinical study, maximum serum VS-6063 (defactinib) concentrations were generally achieved 1 to 2 hours post-dose following single (Day 1) or multiple-dose administration (Day 15) under fasted and fed conditions. Peak and

total exposure ($C_{max}$ and AUC) generally increased with increasing dose across the entire dose range (12.5 to 750 mg) following a single dose on Day 1, and up to 425 mg BID on Day 15. With multiple-dosing exposure was found to be less than proportional with dose above 425 mg BID. Consequently, dose escalation in the fasting cohort was stopped at the 750 mg BID dose and the MTD was not attained. After a single 425 mg dose (recommended phase 2 dose) the $C_{max}$ and AUC were determined to be 552.6 ng/mL and 3314 ng.hr/mL, respectively. Terminal t1⁄2 following a single dose averaged about 9 hours across all treatment groups.

The measured mean free plasma concentration that corresponded to the plasma median effective concentration (EC50) for inhibition of FAK phosphorylation was used as Ceff for human dose projection. Based on this PK/PD modeling, the total blood Ceff of VS-6063 (defactinib) which will cause 50% inhibition of FAK phosphorylation was estimated at a concentration of 160 ng/mL total (95% CI 93.2 to 228 ng/mL) in mice. Taking into account differences in blood to plasma partitioning with VS-6063 (defactinib), the human plasma efficacious free concentration (Ceff or Css,ave) is 13.3 ng/mL or 26 nM to produce 50% inhibition of FAK phosphorylation. Based on estimates from the Phase 1 PK data, the concentration of free and total drug at the end of a 12 hour dosing interval were 25 ng/mL (50 nM) and 250 ng/mL, respectively, for fasted patients at 400 mg BID (the dose used in this study).

Administration of VS-6063 (defactinib) with food at 300 and 425 mg BID delayed time of $C_{max}$ ($T_{max}$) to about 4 hours but did not change exposure significantly.

## 2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the main screening study, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

**In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.**

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

**NOTE:** CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

**NOTE:** Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

**NOTE:** All patients must have signed the relevant treatment consent form

### 2.1 Eligibility Criteria

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_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH screening protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

_____ 2.1.2 Patients must have a tumor that harbors an inactivating mutation in *NF2*. See Appendix III of this sub-protocol for a list of the NF2 mutations and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

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_____ 2.1.4 Patients with known left ventricular dysfunction must have ECHO or a nuclear study (MUGA or First Pass) within 4 weeks prior to registration to treatment and must not have left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN). If the LLN is

not defined at a site, the LVEF must be > 50% for the patient to be eligible.

Date of ECHO/Nuclear Study: _____

**NOTE:** Pre-treatment LVEF determination in patients without known left ventricular dysfuction is NOT otherwise required.

_____ 2.1.5 Patients must not have known hypersensitivity to VS-6063 (defactinib) or compounds of similar chemical or biologic composition.

_____ 2.1.6 Patients must not have a history of upper GI bleeding, ulceration, or perforation within 12 months prior to the first dose of study drug.

_____ 2.1.7 Patients must not have known history of Gilbert's Syndrome.

_____ 2.1.8 Patient must not have a known history of stroke or cerebrovascular accident within 6 months prior to the first dose of VS-6063 (defactinib).

_____ 2.1.9 Patients with history of hypertension should be adequately controlled (BP < 140/90) with appropriate anti-hypertensive therapy or diet.

_____ 2.1.10 Patients must not have prior treatment with a FAK inhibitor (eg. VS-6063 (defactinib) or GSK2256098) and must not be participating or have participated in the COMMAND trial of maintenance therapy of VS-6063 (defactinib) vs. placebo, for mesothelioma.

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_____ 2.1.11 Patients must not be using drugs or foods that are known potent CYP3A4 or CYP2C9 inhibitors or inducers (See Appendix II and Appendix IV of this subprotocol). Substrates of CYP 3A4, 2C9, UGT1A1, P-gp, OATP1B1, and OATP1B3 should be used with caution.

_____ _____

Physician Signature Date

**OPTIONAL:** This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

## 3. VS-6063 (defactinib) Treatment Plan

Rev. 5/16

### 3.1 Administration Schedule

In this study, the dosing regimen for VS-6063 (defactinib) is 400 mg BID. Take VS-6063 immediately following a meal with a full glass of water (approximately 8 ounces). VS-6063 (defactinib) will be administered in continuous 28 day cycles. The dosing regimen is based on the findings of the Phase I FIH study and supporting nonclinical data.

Patients will undergo restaging scans following the completion of every 2 cycles. See Section 3.6 regarding the duration of therapy and procedures for discontinuing treatment.

### 3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

#### 3.2.1 Additional instructions, requirements and exceptions for protocol EAY131-U

**Additional Instructions**

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

**EAY131-U specific expedited reporting requirements:**

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on VS-6063 (defactinib), or within 28 days of the subject's last dose of VS-6063 (defactinib), are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in the MATCH Master protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

**EAY131-U specific expedited reporting exceptions:**

For study Subprotocol U, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event."

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

**NOTE:** The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

**NOTE:** If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be

submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

**NOTE:** Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

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Rev. 8/17
Rev. Add21

## 3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for VS-6063 (defactinib hydrochloride, NSC 781450)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 307 patients. Below is the CAEPR for VS-6063 (defactinib hydrochloride).

**NOTE:** If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

**Version 2.3, April 5, 2019**[1]

| **Adverse Events with Possible Relationship to VS-6063 (defactinib hydrochloride) (CTCAE 5.0 Term) [n= 307]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | |
| | Constipation | | ***Constipation (Gr 2)*** |
| | Diarrhea | | ***Diarrhea (Gr 2)*** |
| Nausea | | | ***Nausea (Gr 2)*** |
| | Vomiting | | ***Vomiting (Gr 2)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | ***Edema limbs (Gr 2)*** |
| Fatigue | | | ***Fatigue (Gr 2)*** |
| INVESTIGATIONS | | | |
| Blood bilirubin increased | | | ***Blood bilirubin increased (Gr 2)*** |
| | Creatinine increased | | |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 2)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | |
| | Dysgeusia | | |
| | Headache | | ***Headache (Gr 2)*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | ***Cough (Gr 2)*** |
| | Dyspnea | | ***Dyspnea (Gr 2)*** |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Adverse events reported on VS-6063 (defactinib hydrochloride) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that VS-6063 (defactinib hydrochloride) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Anemia

**CARDIAC DISORDERS** - Heart failure

**EAR AND LABYRINTH DISORDERS** - Ear pain

**EYE DISORDERS** - Blurred vision; Watering eyes

**GASTROINTESTINAL DISORDERS** - Abdominal distension; Dry mouth; Dyspepsia; Esophageal ulcer; Esophagitis; Flatulence; Gastroesophageal reflux disease; Mucositis oral

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Fever; Malaise; Non-cardiac chest pain

**IMMUNE SYSTEM DISORDERS** - Allergic reaction

**INFECTIONS AND INFESTATIONS** - Catheter related infection; Lung infection; Upper respiratory infection

**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising; Fracture; Injury, poisoning and procedural complications - Other (laceration of scalp); Injury, poisoning and procedural complications - Other (limb injury)

**INVESTIGATIONS** - Alanine aminotransferase increased; Alkaline phosphatase increased; Electrocardiogram QT corrected interval prolonged; Neutrophil count decreased; Platelet count decreased

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hyperglycemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (hypouricemia)

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Back pain; Chest wall pain; Myalgia; Pain in extremity

**NERVOUS SYSTEM DISORDERS** - Intracranial hemorrhage; Lethargy; Peripheral sensory neuropathy; Stroke; Syncope

**PSYCHIATRIC DISORDERS** - Confusion; Psychiatric disorders - Other (mental status changes)

**RENAL AND URINARY DISORDERS** - Acute kidney injury; Hematuria; Proteinuria

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Epistaxis; Pharyngolaryngeal pain; Respiratory failure

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Photosensitivity; Pruritus; Rash maculo-papular

**VASCULAR DISORDERS** - Flushing; Hypertension; Hypotension; Thromboembolic event

**NOTE:** VS-6063 (defactinib hydrochloride) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

## 3.4 Dose Modifications

**All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.**

**All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).**

### 3.4.1 Dose Delays and Dose Modifications:

AEs assessed by the Investigator as exclusively related to underlying disease or medical condition or concomitant treatment will not be taken into consideration for treatment interruption and dose reduction. If treatment must be delayed for reasons other than toxicity, contact the Subprotocol Study Chair to discuss the reasons for delay and plans for resuming study therapy.

Treatment may be delayed up to 14 days (2 weeks) for toxicity resolution. If toxicity does not resolve to eligible levels after 2 weeks, the patient will be taken off study for unacceptable toxicity.

Subjects who experience a toxicity requiring reduction in dose level may continue treatment at the lower dose level until disease progression or unacceptable toxicity. Once the dose has been reduced it may not be re-escalated.

The table below details dosing delays and dose modifications for VS-6063 (defactinib).

| Toxicity Criteria | Dose Modification |
|---|---|
| Persistent grade 2 nonhematological toxicities lasting > 7 days (excluding alopecia, nausea, vomiting, or diarrhea) | Withhold study drug up to 2 weeks until toxicity decreases to ≤ grade 1 or returns to Baseline and resume dosing at current dose.<br>If on resumption of treatment, toxicity returns to ≥ grade 2, withhold treatment up to 2 weeks until toxicity decreases to ≤ grade 1 or returns to Baseline and decrease subsequent dose to 200 mg (1 tablet) BID.<br>If toxicity returns to ≥ grade 2 at reduced dose, permanently discontinue study drug. |
| Grade 3 and 4 non-hematological events (except alopecia, nausea, vomiting, or diarrhea not already maximally medically managed) | Withhold study drug up to two weeks until toxicity decreases to ≤ grade 1 or returns to Baseline and resume dosing at current dose.<br>If on resumption of treatment, toxicity returns to ≥ grade 3, withhold treatment up to 2 weeks until toxicity decreases to ≤ grade 1 or returns to Baseline and decrease dose to 200 mg (1 tablet) BID.<br>If toxicity returns to ≥ grade 3 at reduced dose, permanently discontinue study drug. |
| Hematological toxicities have not been previously reported with VS-6063 (defactinib). The recommendations below are provided as guidance in the event of treatment-related hematological changes. | |
| Grade 3 or 4 neutropenia | Withhold study drug up to 2 weeks until ANC > $1.5x10^9$ cells/L and fever resolved. Reduce dose to 200 mg (1 tablet) BID. If recurs at the reduced dose, permanently discontinue the study drug. |
| Grade 3 or 4 thrombocytopenia | Withhold study drug up to 2 weeks until platelets > $100x10^9$ cells/L. Reduce dose to 200 mg (1 tablet) BID.<br>If toxicity returns to ≥ grade 3 at reduced dose, permanently discontinue study drug. |
| **NOTE: See additional instructions regarding specific toxicities including hyperbilirubinemia in Section 3.4.2.1 below.** | |

### 3.4.2 Additional Toxicity Management Instructions

#### 3.4.2.1 Increased Bilirubin

If the grade 3 or 4 increase in bilirubin is not associated with an increase in AST or ALT, the bilirubin value must return to ≤ grade 2 before resuming study therapy at the current dose level. If on retreatment bilirubin returns to ≥ grade 3, withhold treatment until toxicity ≤ grade 2 or returns to Baseline and decrease dose to 1 tablet (200 mg), BID.

If the bilirubin increases to ≥ grade 2 and is associated with an ≥ grade 2 increase in AST and/or ALT, permanently discontinue study drug.

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#### 3.4.2.2 Nausea

Take VS-6063 immediately following a meal with a full glass of water (approximately 8 ounces). However, subjects who experience nausea following dosing may benefit from eating a few crackers or other small amounts of food before or after taking the study drug. On the basis of Phase I data, initial use of prophylactic premedication was not required. However, prophylactic medications may be used as needed if nausea is found to occur with administration of study drug and cannot be managed with small amounts of food.

#### 3.4.2.3 Hypertension

Minor, generally asymptomatic increases in blood pressure were observed in the Phase I study with VS-6063 (defactinib). Subjects experiencing recurrent, persistent, or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 mmHg if previously within normal limits, should be initiated on antihypertensive therapy according to institutional policies. Study drug should not be interrupted.

For subjects with persistent systolic BP >= 160 mm Hg or diastolic BP > = 100 mm Hg despite optimal antihypertensive therapy, study drug should be interrupted until < 150/100 mm Hg and the dose of study drug should be reduced.

#### 3.4.2.4 Phototoxicity

VS-6063 (defactinib) may cause sensitivity to direct and indirect sunlight. The subjects should be warned to avoid direct sun exposure. When exposure to sunlight is anticipated for longer than 15 minutes, the subject should be instructed to apply factor 30 or higher sunscreen to exposed areas and wear protective clothing and sunglasses.

3.4.2.5 Other

If the subject has requested that study treatment be discontinued due to a toxicity that does not require dosing delays or dose reductions, contact the Subprotocol Study Chair to discuss options for clinical management that may be helpful to support continuation of study therapy.

## 3.5 Supportive Care

3.5.1 All supportive measures consistent with optimal patient care will be given throughout the study. Subjects should receive full supportive care including transfusion of blood and blood products and antibiotics, etc., according to local standards and guidelines. Adequate treatment for nausea, vomiting, and diarrhea is permitted according to institutional guidelines. Take VS-6063 immediately following a meal with a full glass of water (approximately 8 ounces)

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Nausea and emesis:

For nausea and vomiting, treat with standard anti-emetics such as prochloroperazine or ondansetron. Patients should be counseled that taking the medication with food may reduce nausea. The use of prophylactic antiemetics should be considered per standard clinical guidelines. Given the potential for ondansetron to increase QTc prolongation, review baseline QTc EKG prior to initiation of ondansetron and consider follow up EKGs on treatment.

Diarrhea:

For grade 1 diarrhea, symptomatic care such as loperamide (Imodium) or no intervention at investigator judgment. For grade 2 diarrhea, loperamide (4 mg at first onset, then 2 mg every 2-4 hrs until symptom free for 12 hours).

## 3.6 Duration of Agent-specific treatment

VS-6063 (defactinib) will be administered daily by mouth as described in Section 3.1.

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

## 3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

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# 4. Study Parameters

## 4.1 Therapeutic Parameters for VS-6063 (defactinib) Treatment

**NOTE:** In addition to the study parameters listed in the main screening protocol, the below parameters must also be performed for patients receiving VS-6063 (defactinib) treatment.

**NOTE:** All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

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| Test/Assessment | Prior to Registration to Treatment | Treatment | | End of Treatment | Follow Up[F] |
|---|---|---|---|---|---|
| | | Every Cycle, prior to treatment | Every 2 Cycles | | |
| H&P, Weight, Vital signs[A] | X | X[H] | | | X |
| Performance status | X | X[H] | | | X |
| CBC w/diff, plts[B] | X | X[H] | | | X |
| Serum chemistry[B] | X | X[H] | | | X |
| Radiologic evaluation[D] | X | | X[D] | | X[F] |
| β-HCG[C] | X | | | | |
| Toxicity Assessment | | X[H] | | X | X[F] |
| Pill Count/Diary[G] | | X | | X | |
| Concomitant Medications | X | X[H] | | | |
| ECG | X[I] | | | | |
| ECHO/Nuclear Study | X[J] | | | | |
| Rev. 3/17 Tumor biopsy and blood sample for MATCH Master Protocol[E] | | | X | X | |

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

Rev.2/16 B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

Rev.2/16 C. Blood pregnancy test (women of childbearing potential) required prior to beginning treatment.

D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks

before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients removed from study for progressive disease.

Rev. 3/17 E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. See Section 9.3.2.3 of MATCH Master Protocol. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

Rev.2/16 F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but is required every subsequent cycle.

H. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this timepoint: H&P, Weight, Vital signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications. The Toxicity Assessment is not required prior to Cycle 1, but required every subsequent cycle.

I. Within 8 weeks of treatment assignment.

Rev.2/16 J. As required per Section 2.1.4.

## 5. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

### Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

### NCI Supplied Agent(s) – General Information

**Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.**

**Drug Returns:** All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

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**Drug Accountability:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator.

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**Investigator Brochure Availability:** The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the

maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

5.1 VS-6063 (defactinib hydrochloride) (NSC #781450)

5.1.1 Other Names

Defactinib, PF-04554878

5.1.2 Classification

Focal adhesion kinase (FAK) inhibitor

5.1.3 Mode of Action

VS-6063 is an ATP-competitive inhibitor of focal adhesion kinase (FAK) and proline-rich tyrosine kinase 2 (Pyk2). FAK and Pyk2 are members of the same family of nonreceptor protein tyrosine kinases sharing significant sequence homology and are implicated as important integrating molecules in signal transduction cascades.

5.1.4 Storage and Stability

**Storage:** Store VS-6063 tablets at controlled room temperature (15-25°C/59-77°F).

**Stability:** Shelf-life stability studies of VS-6063 tablets are ongoing.

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5.1.5 Dose Specifics

400 mg will be taken every 12 hours immediately following a meal with a full glass of water (approximately 8 ounces).

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5.1.6 How Supplied

VS-6063 tablets are supplied by Verastem, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. VS-6063 is supplied as 200 mg immediate release tablets (white to off-white, oval shaped) packaged in 64-count high density polyethylene (HDPE) bottles. The tablets contain a blend of drug substance, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and magnesium stearate.

The pharmaceutical collaborator does not have stability data to support repackaging VS-6063 tablets in any container other than what is provided.

The active ingredient used for the VS-6063 clinical supplies is the hydrochloride salt.

5.1.7 Route of Administration

Oral.

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5.1.8 Incompatibilities

VS-6063 is metabolized by CYP2C9 and 3A4. Avoid coadministration of strong CYP2C9 and 3A4 inhibitors/inducers. VS-6063 is a weak inhibitor of CYP2C9 and 3A4, a substrate and a weak inhibitor of P-gp, and an inhibitor of OATP1B1, 1B3, and UGT1A1 in vitro. Concomitant administration of substrates for CYP2C9, 3A4, P-gp, OATP1B1, 1B3, and UGT1A1 should be used with caution.

VS-6063 may have the potential to increase warfarin exposure due to a potential drug-drug interaction affecting warfarin's metabolism. An increased level of caution is recommended. If subjects can safely stop taking warfarin, they should do so. If subjects require anti-coagulation, an alternative to warfarin should be considered. Subjects who require anti-coagulation but cannot discontinue warfarin should be monitored closely and have their INRs checked more frequently.

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**NOTE:** Warfarin may not be started while enrolled in the EAY131 study.

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5.1.9 Side Effects

See Section 3.3 for side effects.

## 6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

## 7. References

1. Siesser PM, Hanks SK. The signaling and biological implications of FAK overexpression in cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2006;12(11 Pt 1):3233-3237.
2. Poulikakos PI, Xiao GH, Gallagher R, et al. Re-expression of the tumor suppressor NF2/merlin inhibits invasiveness in mesothelioma cells and negatively regulates FAK. Oncogene. 2006;25(44):5960-5968.

**Molecular Analysis for Therapy Choice (MATCH)**
**MATCH Treatment Subprotocol U: VS-6063 (defactinib) in Patients with Tumors with NF2 Loss**

## Appendix I

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## Patient Pill Calendar

**Pill Calendar Directions**

1. Take your scheduled dose by mouth twice daily at the same time each morning and evening approximately 12 hours between doses.
2. If you forget, the missed tablets should not be taken later.
3. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
4. Swallow tablets whole (do not crush, dissolve, or chew tablets).

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5. Take VS-6063 (defactinib) immediately following a meal with a full glass of water (approximately 8 ounces).
6. Store tablets at room temperature.

## Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each tablet. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

### VS-6063 (defactinib)

| DAY | Date | | | Time tablets taken | | Number of tablets taken | | Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.) |
|---|---|---|---|---|---|---|---|---|
| | Month | Day | Year | AM | PM | AM | PM | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
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| 27 | | | | | | | | |
| 28 | | | | | | | | |

Patient Signature: _____ Date: _____

**Molecular Analysis for Therapy Choice (MATCH)**
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## Appendix II

### Information on Possible Drug Interactions

**Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements**

Rev. 12/16 *The patient _____ is enrolled on a clinical trial using the experimental study drug **VS-6063 (defactinib)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.*

**These are the things that you as a prescriber need to know:**

**VS-6063 (defactinib)** interacts with certain specific enzymes in the liver and transport proteins that help move drugs in and out of cells.

- The enzymes in question are ***CYP 3A4, 2C9, and UGT1A1*.** VS-6063 (defactinib) is metabolized by CYP 3A4 and 2C9 and may be affected by other drugs that inhibit or induce these enzymes. VS-6063 (defactinib) is an inhibitor of CYP 3A4, 2C9, and UGT1A1 and may affect metabolism of other drugs that are substrates for these enzymes.
- The proteins in question are ***P-gp, OATP1B1, and OATP1B3*.** VS-6063 (defactinib) is a substrate of P-gp and may be affected by other drugs that inhibit or induce P-gp. VS-6063 (defactinib) is an inhibitor of P-gp, OATP1B1, and OATP1B3, and may affect transport of other drugs in and out of cells.

**To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet**.

VS-6063 (defactinib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

**These are the things that you and they need to know:**

VS-6063 (defactinib) must be used very carefully with other medicines that need certain **liver enzymes or transport proteins to be effective or to be cleared from your system.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of **CYP 3A4 and 2C9** or substrates of **CYP 3A4, 2C9, UGT1A1, P-gp, OATP1B1, and OATP1B3."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

_____

and he or she can be contacted at

_____.

**STUDY DRUG INFORMATION WALLET CARD**

You are enrolled on a clinical trial using the experimental study drug **VS-6063 (defactinib)**. This clinical trial is sponsored by the NCI. **VS-6063 (defactinib)** may interact with drugs that are **processed by your liver, or use certain transport proteins in your body**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

**VS-6063 (defactinib)** interacts with **CYP 3A4, 2C9, UGT1A1, P-gp, OATP1B1, and OATP1B3**, and must be used very carefully with other medicines that interact with these enzymes.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors of CYP 3A4 and 2C9 or substrates of CYP 3A4, 2C9, UGT1A1, P-gp, OATP1B1, and OATP1B3"**
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

**Molecular Analysis for Therapy Choice (MATCH)**
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## Appendix III

### Actionable Mutations for Sub-Protocol EAY131-U

NF2 is a tumor suppressor gene. Inactivating deleterious mutations could occur anywhere in the coding regions. Instead of listing all possible deleterious mutations, we have implemented a function in MATCHBOX that can identify any point mutations creating stop codons that will lead to premature truncations or any insertions/deletions causing frameshifts, which are predicted to result in a non-functional or absent protein.

Those mutations will be considered to be actionable mutations with level of evidence 3. Variants, including missense mutations, were not included for eligibility if there was a lack of adequate evidence that such variants resulted in loss of function in NF2 gene.

**Molecular Analysis for Therapy Choice (MATCH)**
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## Appendix IV

## CYP3A4 Inducers and Inhibitors

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. The Principal Investigator should be alerted if the subject is taking any agent on these lists.

**List of CYP3A4 Inducing Agents:**

Carbamazepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Modafinil
Naficillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbitol
Phenylbutazone
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Rifapentine
Rofecoxib
St. John's Wort
Sulfadimidine
Sulfinpyrazone
Tipranavir
Troglitazone

**List of CYP3A4 Inhibitors:**

Amiodarone
Cimetidine
Ciprofloxacin
Clarithromycin
Delavirdine
Diethyl-dithiocarbamate
Diltiazem
Erythromycin
Fluconazole
Fluvoxamine
Gestodene
Grapefruit or Grapefruit juice
Indanvir
Itraconazole
Ketoconazole
Mibefradil
Mifepristone
Nefazodone
Nelfinavir
Norfloxacin
Norfluoxetine
Ritonavir
Roxithromycin
Saquinavir
Troleandomycin
Voriconazole
Warfarin
Amprenavir
Atazanavir
Miconazole
Telithromycin
Verapamil