CLINICAL SUBPROTOCOL DAY101-102A

A Phase 2, Subprotocol of DAY101 Monotherapy for Patients with Recurrent, Progressive, or Refractory Solid Tumors with MAPK Pathway Aberrations

Investigational Product:	DAY101
Protocol Number:	DAY101-102a
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Development Phase:	2
Sponsor:	Day One Biopharmaceuticals, Inc. (Day One) 2000 Sierra Point Parkway, Suite 501 Brisbane, CA 94005
Original Protocol	09 February 2021
Protocol Amendment 1.0	01 September 2021
Protocol Amendment 2.0	19 October 2022

Protocol Approval Page

Protocol Title:	A Phase 2, Subprotocol of DAY101 Monotherapy for Patients with Recurrent, Progressive, or Refractory Solid Tumors with MAPK Pathway Aberrations
Protocol Number:	DAY101-102a
Protocol Amendment 2.0	19 October 2022

The current amendment of the protocol has been reviewed and approved.

[redacted]

[redacted]

I have carefully read Protocol DAY101-102a entitled "A Phase 2, Subprotocol of DAY101 Monotherapy for Patients with Recurrent, Progressive, or Refractory Solid Tumors with MAPK Pathway Aberrations". I confirm that I have read and agree to conduct the clinical study as outlined in the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki as amended, and all other applicable regulatory requirements. Furthermore, I understand that the Sponsor, Day One, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee/Human Research Ethics Board (IRB/REB/IEC/HREC) must approve any changes to the protocol in writing before implementation.

I agree to inform all patients that the study drug DAY101 is being used for investigational purposes, and I will ensure that the requirements related to obtaining informed consent and pediatric assent are in accordance with International Council for Harmonisation (ICH) guidelines for GCP and local regulatory requirements.

I agree, on behalf of myself and all other personnel involved in the clinical study who are employed by me, to maintain confidentiality of all information received or developed in connection with this protocol. All data pertaining to this study will be provided to Day One and any presentation or publication of study data will be reviewed by Day One before release.

_____ _____

Principal Investigator's Signature Date

_____

Print Principal Investigator's Name

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol DAY101-102a has been amended to incorporate the following major changes. The changes and rationale for each change are summarized in the table below.

Section(s)	Description of Change	Brief Rationale
Title page	Updated Sponsor address.	Administrative.
Title page, Approval page	Protocol versions will be referred to as protocol amendments.	Revised to align with company formatting.
List of Abbreviations and Definition of Terms	Revised list of abbreviations.	Align with current version of protocol
Synopsis, 3.1	Removed sentence: Patients ages 12 up to < 18 years will be included in the study provided their BSA is ≥ 1.5 m^2. Updated study design schema.	Correction. Sentence was removed as weight-based dosing was added.
Synopsis, 3.1.1	Revised end of study to reflect approximately 25 months after last patient is enrolled.	Corrected study duration.
Synopsis, 4.1, 4.2	Moved all eligibility criteria into sub- protocols.	Restructured eligibility criteria between DAY101-102 and sub- protocols.
Synopsis; 4.1	[redacted]	

Synopsis; 4.2	• Clarified cardiac arrythmias. Added ischemia, ventricular hypertrophy, cardiomyopathy, or conduction disorder [redacted] • Added electrolyte imbalances in serum potassium, magnesium, or calcium that are not currently adequately managed • Added patients with history of acute neurological events (such as intracranial or subarachnoid hemorrhage, stroke, intracranial trauma) within the past 6 months [redacted]	[redacted]

Schedule of Activities (Table 1)	• Addition of Tanner Stage • Addition of bone age • Addition of HIV/hepatitis serology assessments • Removed DAY101 dosing at [redacted] • Removed AEs and concomitant medication on [redacted] • Corrected vital sign footnote • Added: Neurological Examination assessment and timepoints • Removed footnote "c" for ECHO/MUGA assessment; removed assessment at [redacted] • Removed footnote "q" at [redacted] for freshly acquired tumor tissue • Added DAY101 Drug Dispensation/ Return assessment at [redacted] • Clarified footnote "s": tumor tissue archival sample collected preferably within the last 3 years • Clarified that assessments will be performed by an ophthalmologist or a qualified site clinical personnel. • Added "All patients: A baseline complete neurologic examination should be performed by the Investigator and/or a neurologist. Symptom directed neurologic examinations may be completed at subsequent visits. Tissue Agnostic Cohort: Patients with CNS tumors will have complete neurologic examinations performed at baseline and at [redacted] as indicated." • Added: Triplicate ECGs on [redacted]	Editorial changes and corrections throughout Schedule of Activities and footnotes. Per ANSM recommendation, included regular neurologic examinations for patients with CNS tumors who enroll in the Tissue Agnostic Cohort. Per ANSM recommendation, modified protocol to add requested triplicate ECGs.
1.3.1	[redacted] Added results from Study FIREFLY-1/PNOC026 and Study [redacted]	
5.2.1, Table 6	Clarified dosing instructions.	General dosing instructions revised to align with DAY101 programs.

5.2.3	Added guideline for dose modification, inclusive of edema-associated adverse events (AEs).	Per ANSM request, added dose modification guidelines for edema-associated AEs.
5.2.4.1	Clarified assessments will be performed by an ophthalmologist or a qualified site clinical personnel. Clarified discontinuation of DAY101 in the event of retinal detachment diagnosis.	Provided guidance on who may perform ophthalmology examinations and visual symptom assessments. Per ANSM recommendation, revised guidance for retinal detachment.
5.2.4.2 (Table 9)	Added: If a Grade 4 rash recurs at a reduced dose, a second dose reduction is not acceptable, and discontinuation of treatment is required.	Per ANSM recommendations, revised course of action in the case of a Grade 4 rash recurrence.
5.2.4.3	Added text to clarify sunglasses should be worn when exposed to sunlight/UV light. Increased skin protection factor (SPF) to ≥50. Updated the recommendation for prophylactic skin care regimen.	Per ANSM recommendations, added guidance on wearing sunglasses and increased SPF to ≥50. To clarify all patients receiving DAY101 should follow the prophylactic skin care regimen recommendations.
5.2.4.4 (Table 9)	Added: If a Grade 3 or 4 creatine phosphokinase (CPK) elevation is symptomatic, discontinuation of treatment is required.	Per ANSM recommendations, clarified course of action if second occurrence of increase CPK occurs.
5.2.4.4, Table 10	Added bilirubin parameters. Removed “asymptomatic” for ≥ Grade 3 adverse event grading. Clarified if Grade 3 or 4 liver function test (LFT) elevation recurs, a second dose reduction may be considered if asymptomatic and isolated.	Per PCL-Canada recommendations, revised section to include bilirubin assessment guidance. Per ANSM recommendations, revised definition of Grade 3 increased liver transaminases. Also clarified course of action in the case of Grade 3 or 4 LFT elevation.
5.2.4.5	Added QTc prolongation guidance.	Per ANSM recommendation, added guidelines for dose modification and ECG monitoring in the event of QTc prolongation.
5.3.1	Clarified window for recording medications in electronic case report form.	Revised to align between studies.
5.3.2; 5.3.3	Revised text to advise medications that may cause hypomagnesemia or hypermagnesemia and hypophosphatemia should be used with caution.	Per ANSM request, modified concomitant medications.

5.3.4	Added palliative radiotherapy.	To provide guidance on palliative radiotherapy.
5.5.3	Clarified concomitant medications and recommendation of prohibited concomitant medications.	To provide guidance and clarify medications that may not be used when receiving DAY101.
6.6.2	Addition of Tanner Stage	To assess Tanner Stage for patients 12 to <18 years of age at screening and yearly thereafter.
6.6.7	Clarified when neurological examinations should be performed for patients in the Tissue Agnostic Cohort.	Per ANSM recommendation, added neurological examinations more frequently for patients with neurological tumors.
6.7, 6.10, 6.15	Added subheadings to align with DAY101 Master study.	Administrative.
6.17	Modified protocol to include justification of sample blood volumes in the pediatric population	Per Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) recommendation, added language in accordance with the European Commission (EC)'s recommendations for pediatric patients (aged < 18 years).
7.3.3	Clarified pharmacokinetic analyses method.	To clarify validated bioanalytical method will be used and concentrations will be summarized using standard summary statistics.
8.2, 8.2.1, 8.2.1	Revised language to reflect Safety Review Committee and Independent Monitoring Committee (IDMC) will be established.	Per Federal Agency for Medicines and Health Products (FAMHP) request, added the implementation of a IDMC for analysis of cumulative safety data throughout study conduct.
10	Added new citations.	Updated to reflect current version of protocol.
Appendix A	Revised list of medications that have possible CYPs and transporters interactions while using DAY101.	To provide guidance on medications that may have possible interactions while using DAY101.
Appendix B	Added new appendix for medications known to cause QTc prolongation.	Per ANSM recommendation, added guidelines for dose modification and ECG monitoring in the event of QTc prolongation. Included list of medications known to cause QTc prolongation.

Additional minor formatting and editorial changes (not listed in the table above) have been made to improve clarity and to correct grammar and typographical errors. These include revisions to abbreviations and literature references, as applicable.

SYNOPSIS

TITLE:

A Phase 2, Subprotocol of DAY101 Monotherapy for Patients with Recurrent, Progressive, or Refractory Solid Tumors with MAPK Pathway Aberrations

STUDY SITES:

Approximately 15 institutions will participate in this study.

PHASE:

2

OBJECTIVES:

See Study Protocol DAY101-102 (Master Protocol) for a complete list of objectives.

STUDY DESIGN:

This is a Phase 2, multi-center, open-label sub-protocol of Master Protocol DAY101-102, which will enroll patients ≥12 years of age with recurrent or progressive melanoma or solid tumors with BRAF fusion or CRAF/RAF1 fusions or amplification. Patients with these alterations will be identified through molecular assays as routinely performed at Clinical Laboratory Improvement Amendments of 1988 (CLIA) or other similarly certified laboratories. In this sub-protocol, patients will be enrolled into a melanoma cohort or a "tissue agnostic" cohort.

Study DAY101-102a will consist of a screening period, a treatment period, a safety/efficacy follow-up period, and a long-term follow-up period where survival status, and subsequent anticancer therapies will be collected.

DAY101 will be administered to adult patients (≥ 18 years) at 600 mg orally (PO) once weekly (QW), the maximum tolerated dose (MTD) as determined from Takeda Study C28001 ([redacted] on [redacted]. For patients ages 12 to <18 years, DAY101 will be administered at a dose of 420 mg/m^2 PO QW, the recommended Phase 2 dose (RP2D) as determined from the [redacted] study ([redacted] not to exceed 600 mg weekly. Cycles will repeat every 28 days in the absence of disease progression or unacceptable toxicity, withdrawal of consent, or death. Patients will undergo radiographic evaluation of their disease at the end of [redacted] for 1 year and then [redacted] thereafter. Patients will continue DAY101 until radiographic evidence of disease progression by criteria as appropriate for their disease setting, unacceptable toxicity, patient withdrawal of consent, or death. Generally, response assessment will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for solid tumors. Alternative criteria may be used in specific disease settings, such as glioma, where response assessment will be assessed by Response Assessment in Neuro-Oncology (RANO) criteria. Appropriate response criteria for tumors will be described in Appendix B and Appendix C of the Master Protocol.

Patients who have radiographic evidence of disease progression may be allowed to continue DAY101 if, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor.

See Schedule of Activities for further details.

MAJOR ELIGIBILITY CRITERIA:

The eligibility and exclusion criteria listed below are interpreted literally and cannot be waived.

INCLUSION CRITERIA

The following inclusion criteria must be met to be eligible for enrollment in this study:

1. Signed informed consent by patients ≥ 12 years of age; either a Consent or an Assent Form will be provided to the patient based on their capacity, local regulations, and guidelines.
2. Patients must have a report of histologically confirmed diagnosis of melanoma or other solid tumor and a BRAF fusion, CRAF/RAF1 fusion, or CRAF/RAF1 amplifications obtained through a tumor or liquid biopsy as assessed by genomic sequencing, polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or another clinically accepted molecular diagnostic method recognized by local laboratory or regulatory agency
3. Patients must have radiographically documented recurrent or radiographically documented progressive disease that is measurable using the appropriate tumor response criteria (e.g. RECIST version 1.1, RANO). Imaging must be performed within 28 days prior to the first dose of study drug .

[redacted]

5. Archival tumor tissue should be preferably less than 3 years old. If unavailable, a freshly acquired tumor tissue or liquid biopsy obtained at baseline to confirm presence of MAPK alteration is required.

   Note: If archival tissue is unavailable, freshly acquired tumor tissue or liquid biopsy is required at Screening.

   See also requirements to obtain fresh tissue biopsy for pharmacodynamic testing in the Schedule of Activities.
6. Previous chemotherapy and hormone therapy (excluding physiologic replacement) must be completed at least 4 weeks or 5 half-lives, whichever occurs first, prior to initiation of therapy.
7. Previous immunotherapy/monoclonal antibody/targeted therapy use must be completed at least 2 weeks or 5 half-lives (whichever is shorter) prior to initiation of therapy. In addition, radiation therapy to the target lesion must be completed at least 6 months prior to initiation of therapy.
8. All associated toxicity from previous therapies must be resolved to ≤ Grade 1 or considered baseline prior to initiation of therapy.
9. If brain metastases are present, they must have been previously treated and be stable by radiographic imaging (must have imaging taken ≥ 4 weeks from treatment of brain metastasis) AND, if receiving corticosteroids, the patient must be neurologically stable by clinical examination and on a stable or a decreasing dose of corticosteroids within 7 days prior to study start.
10. Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 or 1; For patients <16 years of age, a Lansky Performance Score > 70.
11. Acceptable end-organ function as demonstrated by the following laboratory values:
    - Absolute neutrophil count (ANC) ≥ 1000/μL (neutrophil count may not be supported by hematopoietic growth factors within 2 weeks of the laboratory test)
    - Platelet count ≥ 75,000/μL (platelet count may not be supported by transfusions within 2 weeks of the laboratory test)
    - Hemoglobin ≥ 9 g/dL (hemoglobin may not be supported by transfusion, erythropoietin, or other approved hematopoietic growth factors within 2 weeks of the laboratory test)
    - Serum bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 2 × ULN if patient is known to have Gilbert's Disease as the only underlying hepatic disorder; Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN;
    - Serum creatinine clearance ≥ 60 mL/min/1.73 m^2 calculated according to CKD-EPI (Appendix I of the Master Protocol)

[redacted]

[redacted]

EXCLUSION CRITERIA

Patients who meet any of the following exclusion criteria will not be eligible for enrollment in this study:

1. Prior receipt of any RAS-, RAF-, MEK-, or ERK-directed inhibitor therapy.
2. Known presence of concurrent activating alterations. Examples include, but are not limited, to the following: EGFR, ALK, MET, ROS, FGFR, RET, NTRK, PIK3CA, IDH1/2, and cKIT. Genomic profile of tumor under study will be reviewed by the Sponsor to confirm eligibility.
3. Current enrollment in any other investigational treatment study.
4. Patients with current evidence or a history of serous retinopathy (SR), retinal vein occlusion (RVO), or ophthalmopathy present at screening or baseline who would be considered at risk for SR or RVO.
5. Patients who have an unstable neurological condition, despite adequate treatment (e.g., uncontrolled seizures).

[redacted]

8. Concomitant treatment with strong cytochrome (CYP)2C8 inhibitor and/or inducers within 14 days before initiation of therapy.
9. Concomitant treatment with medications that are predominantly transported by breast cancer resistance protein (BCRP) substrates with a narrow therapeutic index within 14 days before initiation of therapy. Medications that are substrates of CYP2C8 are allowed but should be used with caution.

[redacted]

12. Active, uncontrolled systemic bacterial, viral, or fungal infection.
13. History of any major disease that might interfere with safe protocol participation, as determined by the Investigator (e.g., allogeneic bone marrow transplantation, organ transplantation, or interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis).

Patients with subclinical pneumonitis who have received immunotherapy previously can be included if his/her condition is stable without any medical intervention.

14. History of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens Johnsons syndrome (SJS), or hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any other excipient present in the pharmaceutical form of the investigational medicinal product(s).
15. History of second malignancy within 3 years prior to study treatment except for curatively treated cervical cancer *in situ*, non-melanoma skin cancer, or superficial bladder cancer.

[redacted]

PLANNED SAMPLE SIZE:

Up to 43 patients will be enrolled. Up to 18 patients will be enrolled in the melanoma cohort and up to 25 patients will be enrolled in the "tissue agnostic" cohort.

INVESTIGATIONAL DRUG:

DAY101 for oral dosing is provided as a white to off-white [redacted] powder as a 100 mg immediate-release tablet. The 100 mg tablets are red to yellowish-red oval tablets. All products are labeled DAY101.

TREATMENT PROCEDURES:

Patients will initiate treatment at 600 mg QW for adults ≥ 18 years. Adolescents (12 to <18 years) will initiate treatment at 420 mg/m^2 PO QW, not to exceed 600 mg weekly. Each cycle will consist of 28 days of weekly dosing.

Individual patients will continue DAY101 using QW dosing until radiographic evidence of disease progression by criteria as appropriate for their disease setting (e.g., RECIST v1.1, RANO), unacceptable toxicity, patient withdrawal of consent, or death. Patients who demonstrate radiological progression may be allowed to continue DAY101 if, in the opinion of the Investigator and approval by the Sponsor, the patient is deriving clinical benefit from continuing study treatment. Disease assessments for patients being treated beyond progression should continue as per regular schedule.

STUDY ASSESSMENTS:

See Study Protocol DAY101-102 (Master Protocol) for study assessments across all sub-protocols. Additional study assessments included in this sub-protocol will be specified herein.

For this sub-study, blood for PK assessments will be collected as follows: [redacted]. The complete sampling details for PK blood samples is described in Table 10.

All patients taking protocol therapy will have their imaging scans reviewed by a site or local radiologist. Copies of all eligibility, baseline, and on-treatment patient scans, as well as historical scans from the 12-month period immediately prior to the eligibility scan (if available), will be transferred to the central imaging lab for potential future evaluation as specified in the Imaging Manual.

End of Study and Length of Study:

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 25 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

STATISTICAL METHODS:

Sample Size Considerations:

Simon's 2-stage design (Simon, 1989) will be used to determine whether DAY101 has sufficient anticancer activity to warrant further development for each biomarker selected cohort. Enrollment per cohort may be terminated early independently of each other. No adjustment for multiple hypothesis testing will be made if both cohorts complete enrollment.

In the melanoma cohort, up to 7 patients will be enrolled in Stage 1. If no patients achieve a complete response (CR) or partial response (PR); confirmed or unconfirmed) within a cohort, then enrollment within that cohort will terminate. If at least 1 patient achieves CR or PR, 11 additional patients will be enrolled within the cohort in the Stage 2. The null hypothesis assumes a true overall response rate (ORR) of less than 10%, and an alternative hypothesis of an ORR of 10% or more. At a 1-sided alpha of < 0.10, there is 80% power for this cohort, if the true ORR is 30%.

In the "tissue agnostic" cohort, up to 10 patients will be enrolled in Stage 1. If at least 2 patients achieve a CR or PR, an additional 15 patients will be enrolled within the cohort in the second stage. The null hypothesis assumes a true ORR of less than 10% and an alternative hypothesis of an ORR of 10% or more. At a 1-side alpha of < 0.1, there is 81% power for this cohort, if the true ORR is 30%

The Sponsor may consider replacing the patient if the patient is not considered evaluable for response assessment in the Simon Stage 1. The stage 2 will not be activated if the stage 1 minimum number of responses (as shown in table below) is not met and all patients have been followed for at least 6 months.

	Null/Alternative Hypotheses	**Study Power**	**Study Alpha (1-sided)**	**Stage 1 n (Minimum Number of Responses to Move to Stage 2)**
Melanoma cohort	[redacted]	[redacted]	[redacted]	[redacted]
Tissue agnostic cohort	[redacted]	[redacted]	[redacted]	[redacted]

Analysis Methods:

For the primary analysis of the primary endpoint, for both cohorts, a 90% exact confidence interval (CI) will be calculated. See Study Protocol DAY101-102 (Master Protocol) for a description of analysis methods, including efficacy, safety, and pharmacokinetic analyses.

Efficacy Analyses

See Study Protocol DAY101-102 (Master Protocol) for a description of analysis methods for efficacy.

Safety Analyses

See Study Protocol DAY101-102 (Master Protocol) for a description of analysis methods for safety.

Pharmacokinetic Analyses

Plasma concentrations of DAY101 will be analyzed at specified time points using validated bioanalytical methods. Plasma concentrations will be summarized by nominal sample time using standard summary statistics for PK concentrations.

SCHEDULE OF ACTIVITIES

Scheduled activities will be performed in Study DAY101-102a (Monotherapy Sub-protocol) as outlined in Table 1. Every effort should be made to ensure that each protocol-specific procedure is completed as described. Additional details regarding study procedures are included in Section 6 of the Master Protocol.

Table 1: Schedule of Activities

Assessment	[redacted]
Informed consent/ assent[b]	
Demographics	
Medical History	
ECOG or Lansky (for patients <16 years of age)	
Physical examination[c]	
Neurologic Examination[d]	
Dermatologic Examination[d]	
Bone Age[e]	
Tanner Staging[f]	
Vital signs[g]	
12-lead ECG in triplicate[g]	
Hematology[h]	
Chemistry[h]	
Creatine phosphokinase[h]	
Coagulation Panel (APTT/INR)[i]	

Assessment	[redacted]
Thyroid function test[i]	
HBcAb, HBsAg, HCV RNA[j]	
HIV-1 Ab, HIV-2 Ab, HIV viral load and CD4+ T cell count[j]	
Echocardiogram/MUGA[k]	
Ophthalmologic exam[l]	
Visual symptom assessment[m]	
Pregnancy test[n]	
Adverse events[o]	
Concomitant medication[p]	
Tumor assessment CT/MRI[q]	
Archival tumor tissue samples[r]	
Freshly acquired tumor tissue sample (PD analysis) [s,t]	
PK Sample[u, v]	
ctDNA[v]	
Additional anticancer treatment and survival status[w]	
DAY101 dosing[x]	

Assessment	[redacted]
DAY101 Drug Dosing Diary[y]	
DAY101 drug Dispensation/Return[z]	

[a] Results of screening assessments must be reviewed by Investigator before patient enrollment to confirm that the patient meets the eligibility criteria.
[b] Informed consent may be obtained greater than [redacted] but must be provided before any study-specific procedures are performed; however, evaluations performed as part of routine care prior to informed consent can be utilized as screening evaluations if permitted by site IRB/IEC policies. Assessments will be performed at the end of [redacted] Assessments are to be performed on or up to 7 days before the next cycle. For CT/MRI, assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is discontinued. To ensure image consistency, the same imagine modalities and acquisition protocols used at Screening are to be used for subsequent tumor assessments.
[c] A complete physical examination, including weight, height, and vital signs will be performed [redacted] for all subjects. At subsequent physical exams only patients ages 12 to <18 should have height and weight collected. The physical exams will take place prior to the start of dosing of each [redacted]; otherwise, a symptom-directed physical examination will be done.
[d] All patients: A baseline complete neurologic examination should be performed by the Investigator and/or a neurologist. Symptom directed neurologic examinations will be completed at subsequent visits as indicated. A baseline complete dermatologic examination should be performed by the Investigator and/or a dermatologist. Symptom directed dermatologic examinations will be completed at subsequent visits as indicated. Tissue Agnostic Cohort: Patients with CNS tumors will have complete neurologic examinations performed at baseline and at subsequent visits as indicated.
[e] All patients aged 18 years or less should have an assessment of bone age at baseline via bone age radiograph of the left wrist. For patients aged 12-18 years of age without epiphyseal closure at baseline, bone age via radiograph should be assessed [redacted] thereafter.
[f] For patients 12 to < 18 years of age, pubertal stage will be measured [redacted] thereafter. For female patients, age at menarche will be recorded. Assessments will occur while on active treatment through sexual maturity. Refer to Study Protocol DAY101-102 (Master Protocol Section 6.9) for Tanner Staging details.
[g] Vitals performed on days where pharmacokinetic (PK) collection occurs should be performed prior to collection. ECGs should be collected immediately before PK sample collections on days/timepoints when PK sampling occurs (within 15 minutes prior to the PK collection). Patients will rest at least 5 minutes prior to obtaining ECGs. Refer to Section 6.18 for PK sampling details.
[h] Assessment will be performed at [redacted]
[i] Assessment will be performed at [redacted] and as clinically indicated.
[j] Serology testing as defined according to local guidelines.
[k] An echocardiogram or MUGA will be performed at screening, prior to DAY101 dosing at [redacted], or more frequently if clinically indicated. If the LVEF is found to have declined below the lower limit of normal or have declined ≥ 10% during the study, a re-examination needs to be performed within 2 weeks. Must use the same assessment (ECHO or MUGA) at screening and throughout the study.

[l] For ophthalmologic examinations, a full examination by an opthalmologist or other qualified site clinical personnel will be conducted at screening and as clinically indicated if changes in visual symptoms occur throughout the study.
[m] Investigator or qualified site staff will inquire for changes in visual symptoms at every visit (from [redacted]). If change and/or abnormality is reported, this should be recorded as an adverse event and the patient should be referred to an ophthalmologist or other qualified site clinical personnel for further examination.
[n] Assessment will be performed predose at all in-clinic visits and at other timepoints indicated in the Schedule of Activities, or if clinically indicated on patients of child-bearing potential only.
[o] See Study Protocol DAY101-102 (Master Protocol) Section 8.1.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) for instructions regarding AE collection.
[p] Document concomitant medication taken from [redacted]
[q] Assessments will be performed at the end of [redacted] Assessments are to be performed on or up to 7 days before the next cycle. For CT/MRI, assessments are to be performed per the protocol-defined schedule regardless of whether study treatment is discontinued. To ensure image consistency, the same imagine modalities and acquisition protocols used at Screening are to be used for subsequent tumor assessments. For patients who discontinue study treatment before radiographic progressive disease, tumor assessment will progress accordingly as if on study treatment and these patients will be requested to return to site for continued monitoring and assessment.
[r] A tumor tissue archival sample which preferably has been collected within the last 3 years. See Section 6.4 and Laboratory Manual for specific instructions.
[s] A freshly acquired tumor tissue sample collected at screening may also be used for assessment of ERK phosphorylation status (as part of the PD analysis) and ERK-regulated gene expression. If no fresh tumor tissue sample was collected at [redacted] a sample will be taken [redacted] if accessible and can be safely performed. An additional on-treatment tumor sample will be collected [redacted], if accessible and can be safely performed. Fresh tumor tissue collection is considered optional for patients 12 to < 18 years of age.
[t] Refer to Table 10 for PK blood sample schedule. The complete sampling details for PK blood samples will be described in the Laboratory Manual.
[u] PK samples will also be collected if a serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR) occurs.
[v] Additional patient blood samples will be collected by blood draw prior to start of any new therapy.
[w] Patients will be contacted every [redacted] after Safety Follow-up visit until death, these data may be obtained by phone.
[x] DAY101 will be administered in-clinic on [redacted]. On days not in-clinic, DAY101 will be taken once weekly at home until study treatment is discontinued. In the event that the in-clinic visit does not occur on the exact Visit Day as shown in Schedule of Activities [redacted], dosing should be withheld until patient is in the clinic and completes necessary predose visit activities. Note: Within the Schedule of Activities table above at [redacted], dosing is indicated at [redacted], however, DAY101 will continued to be taken weekly at home unless instructed otherwise by the Investigator. Patients will return unused drug at the start of each cycle. No dosing will occur at the EOT visit, only study drug return will take place.
[y] The study diary will be provided at [redacted]. The study diary will be completed by the patient, or patient's parent or legal guardian, for every dose of study drug administered starting at [redacted] The Investigator or study staff should review diary entries for compliance, in particular for any potential missed doses, at every in-clinic, or remote visit. Study diary from last cycle should be returned and reviewed at [redacted]
[z] DAY101 is to be dispensed to patients [redacted] and unused drug should be returned at the start of the following cycle. Study drug from last cycle should be returned at [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from time zero to t
BCRP	breast cancer resistance protein
BCVA	best corrected visual acuity
BP	blood pressure
BRAF	v-raf murine sarcoma viral oncogene homolog B
BSA	body surface area
BUN	Blood urea nitrogen
C	cycle
CI	confidence interval
CKD	chronic kidney disease
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRAF	v-raf murine sarcoma viral oncogene homolog C
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
CYP	cytochrome P450
D	Day
DMC	Data Monitoring Committee
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardiogram
eCRF	electronic case report form
ECHO	echocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
[redacted]	
ERK	extracellular signal-related kinase
FDA	Food and Drug Administration

Abbreviation or Term	Definition
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence *in situ* hybridization
GCP	Good Clinical Practices
HREC	Human Research Ethics Board
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
LGG	low-grade glioma
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	Multiple-gated acquisition
NCI	National Cancer Institute
NSCLC	non small cell lung carcinoma
ORR	overall response rate
PCR	polymerase chain reaction
pERK	phosphorylated ERK
PFS	progression-free survival
PK	pharmacokinetic(s)
pLGG	pediatric low-grade glioma
PO	*per os*, orally
PR	partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
Q2D	every other day
QT_c	QT interval corrected for heart rate
QT_cF	QT interval corrected for heart rate by Fridericia's formula
QW	once weekly
RAF1	Raf-1 Proto-Oncogene, Serine/Threonine Kinase
RANO	Response Assessment in Neuro-Oncology

Abbreviation or Term	Definition
RDD	rhegmatagenous retinal detachment
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RPED	retinal pigment epithelium disorder
R/R	relapsed or refractory
RVO	retinal vein occlusion
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SJS	Stevens Johnsons syndrome
SPF	Skin protection factor
SR	serous retinopathy
SRD	serous retinal detachment
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	tetraiodothyronine
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
t_{max}	time to reach maximum drug concentration
TPCV	thioguanine, procarbazine, lomustine, and vincristine
TTR	time to response
ULN	upper limit of normal
UV	ultraviolet
WHO	World Health Organization

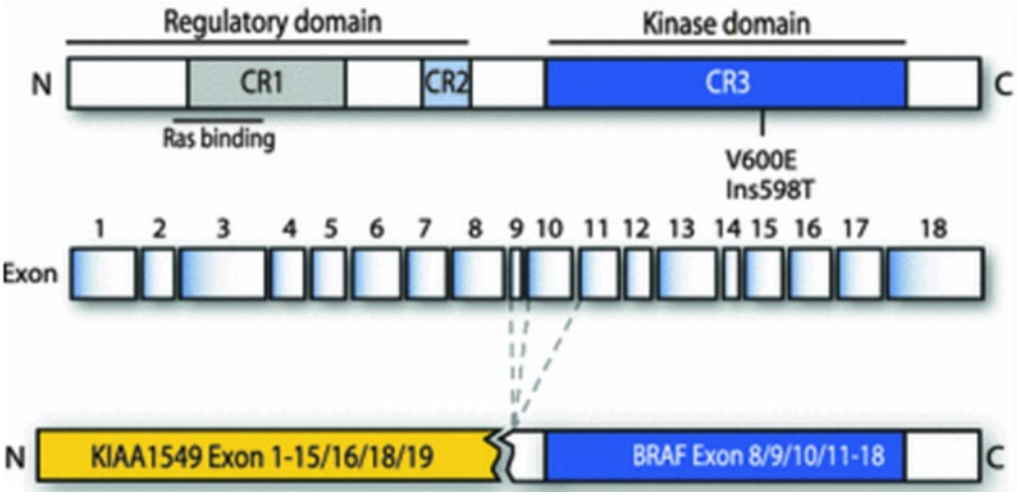
1. INTRODUCTION

See Study Protocol DAY101-102 (Master Protocol).

1.1. Background on Disease

Oncogenic v-raf murine sarcoma viral oncogene homolog B (BRAF) fusions originate from genomic rearrangements placing the 3' portion of the BRAF gene encoding the kinase domain behind another gene at the 5' position. The rearrangements result in the expression of oncoproteins that are constitutively active due to loss of the auto-inhibitory domain of BRAF and whose expression is controlled by the promoter of the 5' partner (Lu et al. 2017).

Figure 1: Mechanism of Fusion Oncogene Action



Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog B.
Source: Jones et al. 2012.

BRAF fusions involving the intact and in-frame BRAF kinase domain were observed in approximately 0.3% of samples analyzed with Foundation Medicine's FoundationOne™ comprehensive genomic profiling (55/20,537) and MSK-IMPACT™ testing (33/10,945), although proportion varies accordingly with tumor histology (Ross et al. 2016, Zehir et al. 2017). BRAF fusion alterations are reported in 3% (14/531) of melanoma, 2% (3/1062) of glioma and approximately 1% in thyroid, pancreatic, non-small cell lung carcinoma (NSCLC), and colorectal cancers (Ross et al. 2016). Given their rarity, the significance of BRAF fusions for clinical outcome is unknown. However, these incidences of BRAF fusions were assessed in patients primarily with relapsed/refractory or advanced cancers whose overall prognostic outcome is generally poor.

v-raf murine sarcoma viral oncogene homolog C (CRAF)/ Raf-1 Proto-Oncogene, Serine/Threonine Kinase (RAF1) fusions, while rare, have also been reported in low-grade glioma (LGG) (Jones et al. 2009, Ryall et al. 2020) and melanoma (Williams et al. 2020). These fusions have also been shown to upregulate the mitogen-activated protein kinase (MAPK) pathway signalling (Jain et al. 2017, Ryall et al. 2020).

To date, there are no approved therapies specifically targeting treatment of adult or pediatric patients with oncogenic BRAF or CRAF fusion-positive tumors. The 3 Food and Drug Administration (FDA)-approved treatments for tumors with BRAF V600E/K mutations -

vemurafenib, dabrafenib, and encorafenib (Type-I BRAF inhibitors) are inappropriate for use in treatment of BRAF or CRAF fusions due to the potential for paradoxical activation of the MAPK pathway associated with dimerization with RAF in wild-type BRAF settings (Sanchez et al. 2008). Type-I BRAF inhibitors have been shown to result in paradoxical activation of pediatric low-grade glioma (pLGG) models driven by the KIAA1549:BRAF fusion and accelerate the growth of tumor models driven by the KIAA1549:BRAF fusion. Clinical proof of concept for this phenomenon occurred in 2014 when the multikinase inhibitor sorafenib, which blocks BRAF V600 in a manner similar to other Type-I BRAF inhibitors, was studied in children with pLGGs and produced unexpected and unprecedented acceleration in tumor growth. This effect was later found to be related to paradoxical extracellular signal-related kinase (ERK) activation (Karajannis et al. 2014). Although currently approved mitogen-activated protein kinase (MEK) inhibitors (cobimetinib, trametinib, and binimetinib) can block MAPK signalling resulting from BRAF or CRAF fusions, they do not directly inhibit RAF, and are associated with significant cardiac, dermatologic, and ophthalmologic toxicities. Use of these MEK inhibitors is still considered investigational in BRAF or CRAF fusion tumors.

Standard of care for adult patients with advanced cancer varies across tumor types. Most commonly, BRAF fusions have been reported in melanoma, LGG, and thyroid cancer. CRAF fusions, while rare, have been reported in melanoma and LGG. As an example, a summary table of systemic treatment regimen and outcome for adult patients based on literature and National Comprehensive Cancer Network (NCCN) Guidelines 2020 is provided in Table 2. Treatment for advanced cancers in pediatric patients are poorly studied given the rarity of these cancers in general and carcinoma histology. Of the targeted therapies approved for treatment of melanoma and thyroid carcinoma in adults, only ipilimumab, selpercatinib, dabrafenib/trametenib are indicated for treatment of certain pediatric patients. After standard-of-care treatment is exhausted for adults, new therapies are required for this rare population with limited treatment options.

Recurrent rearrangements in RAF have been found to occur in advanced prostate cancers, gastric cancers and melanoma (Palanisamy et al. 2010). Beyond BRAF fusions, CRAF/RAF1 fusions have also been detected in melanoma and LGG and while rare, these can also constitutively activate the MAPK pathway (Williams et al. 2020, Ryall et al. 2020). Thus, inhibition of CRAF/RAF1 fusions with a Type II pan-RAF inhibitor such as DAY101 could be a therapeutic strategy to target tumors harboring CRAF/RAF1 fusions.

Lastly, emerging research has identified a unique subset of urothelial tumors with focal amplification of the RAF1 kinase gene. RAF1-amplified tumors have activation of the RAF/MEK/ERK signaling pathway and exhibit a luminal gene expression pattern. Genetic studies demonstrate that RAF1-amplified tumors are dependent upon RAF1 activity for survival. These data identify *RAF1* as a novel dependency in a subset comprising nearly 12% of urothelial tumors and suggest that targeting RAF1-mediated signaling represents a rationale therapeutic strategy (Bekele et al. 2021).

Table 2: Summary of Systemic Treatment Regimen and Outcome in Tumors with BRAF Fusions in Adult Patients

Tumor Type	Systemic Therapy	Regimen	Outcome
Melanoma	1st line	Nivolumab[a], Pembrolizumab[b,e]	ORR (range): 32.9–45% Median OS (range): 36.9 mo[1] –NR[5]
		Nivolumab and Ipilimumab[c]	ORR, 58% (95% CI: 53−64)[1] Median OS > 60 mo (95% CI: 38.2 to NR)[1]
	2nd line	Nivolumab[3], Pembrolizumab[d, f]	ORR (range): 21–32% Median OS (range): 13.4 mo–15.7 mo
Low-Grade Glioma	1st line[g]	Temozolomide (TMZ), or Procarbazine, Lomustine, and Vincristine (PCV)	ORR: (range) - TMZ (43–54%), - PCV (59–63%) Median PFS: (range) - TMZ (11.5 mo, 31 mo), - PCV (20 mo, 30.7 mo)
RAFi Refractory Thyroid Carcinoma	1st line[h]	Tyrosine Kinase Inhibitor: - MTC - Vandetanib, Cabozatinib, Praseltinib, Selpercatinib; - DTC - Sorafenib, Lenvatinib	ORR: (range) - MTC (28–69%), - DTC (12.2–64.8%) Median PFS: (range) - MTC (11.2 mo, 30.5 mo), - DTC (10.8 mo, 18.3 mo)
	2nd line[i]	Chemotherapy: bleomycin, doxorubicin, platinum compound, etoposide	Limited to no response. ORR 37% observed in a small study with doxorubicin based on WHO criteria.

Abbreviations: CI, confidence interval; DTC, differentiated thyroid carcinoma; mo, months; MTC, medullary thyroid cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; WHO, World Health Organization.
Source: [a]Opdivo Prescribing Information, [b]Robert et al. 2019, [c]Weber et al. 2014, [d]Ribas et al. 2015, [e]Schacter et al. 2017, [f]Hamid et al. 2017, [g] Taal et al. 2011 (no treatment considered standard), [h]Lirov et al. 2017, [i]Sherman et al. 2010

1.2. Background on DAY101

See Study Protocol DAY101-102 (Master Protocol).

1.3. Study Rationale and Dose Justification

1.3.1. Study Rationale

The Type-II BRAF inhibitors have been shown preclinically to inhibit both BRAF V600 mutations, BRAF fusions, and CRAF (Botton et al. 2019, Sun et al 2017).

Case reports have demonstrated that inhibitors of the MAPK pathway have anti-tumor activity against different BRAF fusions and tumor histology (Spitzoid melanoma patient with ZKSCAN1:BRAF, malignant spindle cell tumor with KIAA1549:BRAF) (Subbiah et al. 2014, Menzies et al. 2015).

[redacted]. Centrally reviewed radiographic assessments are available from 9 patients enrolled into the dose escalation portion of the study (Wright et al. 2020). Eight of the 9 patients harbored a RAF fusion (7 harbored the canonical KIAA1549:BRAF fusion and

one harbored a SRGAP3-RAF1 gene fusion). Five of 8 (63%) patients with a RAF fusion have achieved a complete response (CR) or partial response (PR) with a median time to response (TTR) of 10.5 weeks. In addition, 77 pLGG patients have been dosed with DAY101 in Arm 1 of the FIREFLY-1/PNOC026 study ([redacted] Preliminary efficacy and safety data have been noted in the master protocol.

The purpose of this study is to additionally evaluate the efficacy and safety of DAY101 as monotherapy in the treatment of adults and adolescents with relapsed, refractory solid tumors and BRAF or RAF1 fusions or RAF1 amplifications who have exhausted standard of care treatments available, including locally directed therapy, such as surgery or radiotherapy.

1.3.2. Justification for Dose

See Study Protocol DAY101-102 (Master Protocol).

1.3.3. Benefit/Risk

See Study Protocol DAY101-102 (Master Protocol).

2. STUDY OBJECTIVES

See Study Protocol DAY101-102 (Master Protocol) for a complete list of objectives and endpoints.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase 2, multi-center, open-label sub-protocol of Master Protocol DAY101-102, which will enroll patients ≥12 years of age with recurrent or progressive melanoma or solid tumors with BRAF fusion or CRAF/RAF1 fusions or amplification. Patients with these alterations will be identified through molecular assays performed at Clinical Laboratory Improvement Amendments of 1988 (CLIA) or other similarly certified laboratories. Patients will be enrolled into either a melanoma cohort or a "tissue-agnostic" cohort.

The study design will consist of a screening period, a treatment period, a safety follow-up period, and a long-term follow-up (LTFU) period where survival status, and subsequent anticancer therapies will be collected.

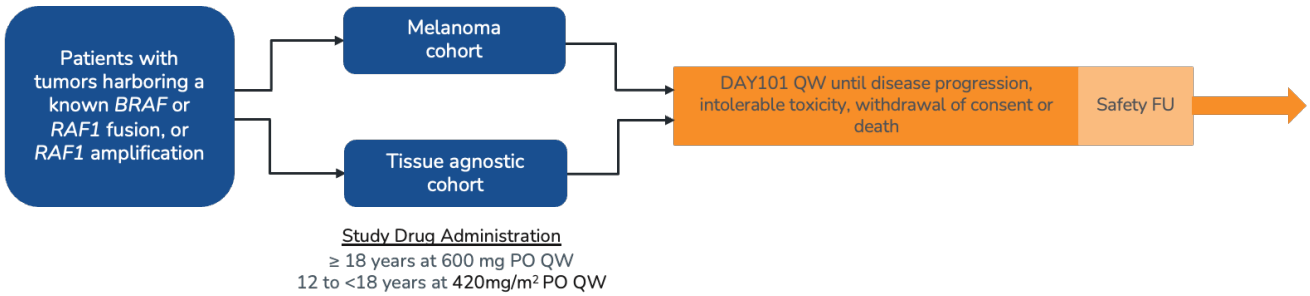
DAY101 will be administered to adult patients (≥ 18 years) at 600 mg orally (PO) once weekly (QW), the maximum tolerated dose (MTD) as determined from Takeda Study C28001 ([redacted] on [redacted]. For patients ages 12 to <18 years, DAY101 will be administered at a dose of 420 mg/m^2 PO QW, the recommended Phase 2 dose (RP2D) as determined from the [redacted] study ([redacted] not to exceed 600 mg weekly. Treatment cycles will repeat every 28 days in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or death. Patients will undergo radiographic evaluation of their disease at baseline, and then at the end of [redacted] for 1 year and then [redacted] thereafter.

Patients who have radiographic evidence of disease progression may be allowed to continue DAY101 if, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor.

Generally, response assessment will be performed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for solid tumors and Response Assessment in Neuro-Oncology (RANO) for central nervous system (CNS) tumors. Appropriate response criteria for tumors are described in Appendix B and Appendix C of the Master Protocol DAY101-102.

See Schedule of Activities for further details. The study design schema is shown in Figure 2.

Figure 2: Study Design Schema



Abbreviations: FU, follow-up; PO, by mouth or orally; QW, once weekly

3.1.1. End of Study and Length of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or safety follow-up is received from the last patient, whichever occurs later. The end of Study DAY101-102a is expected to occur 25 months after the last patient is enrolled. In addition, the Sponsor may decide to terminate this study at any time.

The total length of this study, from screening of the first patient to the end of study, is expected to be approximately 4 years.

3.1.2. Number of Patients

Up to 43 patients will be enrolled. Up to 18 patients will be enrolled in the melanoma cohort, and up to 25 patients will be enrolled in the “tissue agnostic” cohort.

3.2. Investigational Sites

Approximately 15 institutions will participate in this study.

4. SELECTION OF STUDY POPULATION

Potential patients and/or their parents must sign an informed consent form (ICF) and pediatric assent form, where applicable, before any study-specific screening tests may be conducted.

The eligibility and exclusion criteria listed below are interpreted literally and cannot be waived.

4.1. Inclusion Criteria

The following inclusion criteria must be met to be eligible for enrollment in this study:

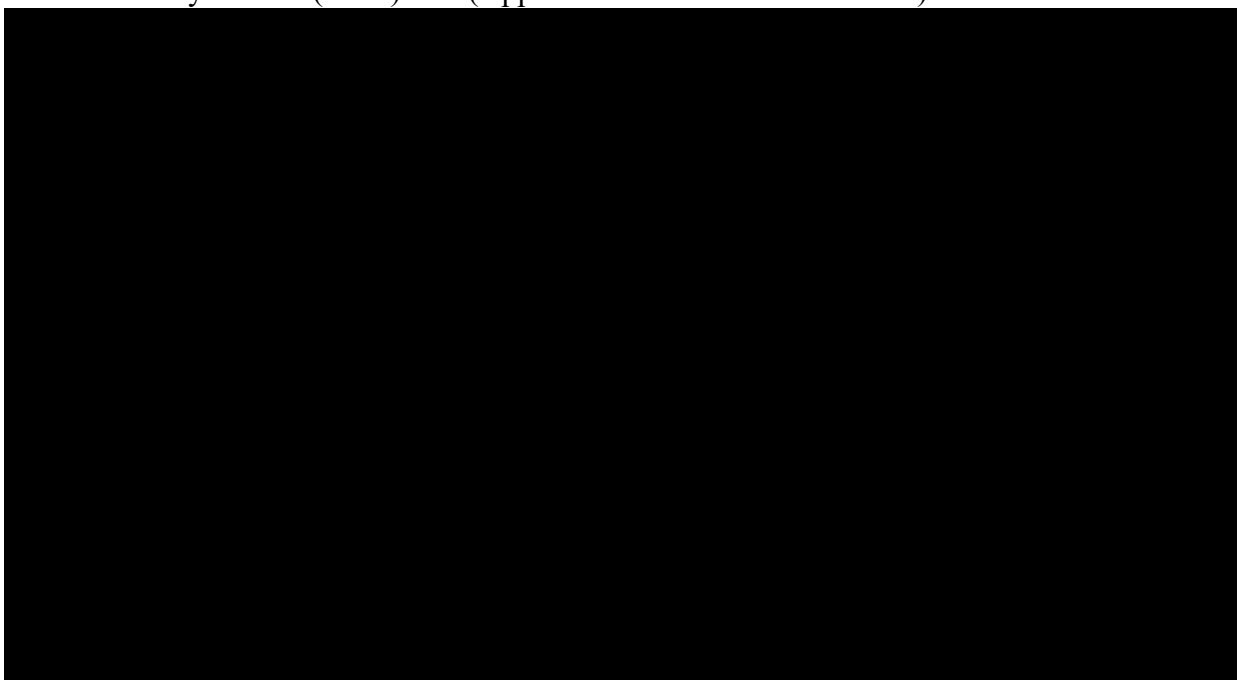
1. Signed informed consent by patients ≥ 12 years of age; either a Consent or an Assent Form will be provided to the patient based on their capacity, local regulations, and guidelines.
2. Patients must have a report of histologically confirmed diagnosis of melanoma or other solid tumor and a BRAF fusion, CRAF/RAF1 fusion, or CRAF/RAF1 amplifications obtained through a tumor or liquid biopsy as assessed by genomic sequencing, polymerase chain reaction (PCR), fluorescence *in situ* hybridization (FISH), or another clinically accepted molecular diagnostic method recognized by local laboratory or regulatory agency.
3. Patients must have radiographically documented recurrent or radiographically documented progressive disease that is measurable using the appropriate tumor response criteria (e.g. RECIST version 1.1, RANO). Imaging must be performed within 28 days prior to the first dose of study drug.

5. Archival tumor tissue should be preferably less than 3 years old. If unavailable, a freshly acquired tumor tissue biopsy or liquid biopsy obtained at baseline to confirm presence of MAPK alteration is required .

   Note: If archival tissue is unavailable, freshly acquired tumor tissue or liquid biopsy is required at Screening.

   See also requirements to obtain fresh tissue biopsy for pharmacodynamic testing in the Schedule of Activities.
6. Previous chemotherapy and hormone therapy (excluding physiologic replacement) must be completed at least 4 weeks or 5 half-lives, whichever occurs first, prior to initiation of therapy.
7. Previous immunotherapy/monoclonal antibody/targeted therapy use must be completed at least 2 weeks or 5 half-lives (whichever is shorter) prior to initiation of therapy. In addition, radiation therapy to the target lesion must be completed at least 6 months prior to initiation of therapy.
8. All associated toxicity from previous therapies must be resolved to ≤ Grade 1 or considered baseline prior to initiation of therapy.

9. If brain metastases are present, they must have been previously treated and be stable by radiographic imaging (must have imaging taken ≥ 4 weeks from treatment of brain metastasis) AND, if receiving corticosteroids, the patient must be neurologically stable by clinical examination and on a stable or a decreasing dose of corticosteroids within 7 days prior to study start.
10. Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 or 1; For patients < 16 years of age, a Lansky Performance Score > 70.
11. Acceptable end-organ function as demonstrated by the following laboratory values:
    - Absolute neutrophil count (ANC) ≥ 1000/μL (neutrophil count may not be supported by hematopoietic growth factors within 2 weeks of the laboratory test)
    - Platelet count ≥ 75,000/μL (platelet count may not be supported by transfusions within 2 weeks of the laboratory test)
    - Hemoglobin ≥ 9 g/dL (hemoglobin may not be supported by transfusion, erythropoietin, or other approved hematopoietic growth factors within 2 weeks of the laboratory test)
    - Serum bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 2 × ULN if patient is known to have Gilbert's disease as the only underlying hepatic disorder; Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN.
    - Serum creatinine clearance ≥ 60 mL/min/1.73 m^2 calculated according to chronic kidney disease (CKD)-EPI (Appendix I of the Master Protocol)



4.2. Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible for enrollment in this study:

1. Prior receipt of any RAS-, RAF-, MEK-, or ERK-directed inhibitor therapy.
2. Known presence of concurrent activating alterations. Examples include, but are not limited, to the following: EGFR, ALK, MET, ROS, FGFR, RET, NTRK, PIK3CA, IDH1/2, and cKIT. Genetic profile of tumor under study will be reviewed by the Sponsor to confirm eligibility.
3. Current enrollment in any other investigational treatment study.
4. Patients with current evidence or a history of serous retinopathy (SR), retinal vein occlusion (RVO), or ophthalmopathy present at screening or baseline who would be considered at risk for SR or RVO.
5. Patients who have an unstable neurological condition, despite adequate treatment (e.g., uncontrolled seizures).

8. Concomitant treatment with strong cytochrome (CYP)2C8 inhibitor and/or inducers within 14 days before initiation of therapy.
9. Concomitant treatment with medications that are predominantly transported by breast cancer resistance protein (BCRP) substrates with a narrow therapeutic index within 14 days before initiation of therapy. Medications that are substrates of CYP2C8 are allowed but should be used with caution.

12. Active, uncontrolled systemic bacterial, viral, or fungal infection.
13. History of any major disease that might interfere with safe protocol participation, as determined by the Investigator (e.g., allogeneic bone marrow transplantation, organ transplantation, or interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis). Patients with subclinical pneumonitis

who have received immunotherapy previously can be included if his/her condition is stable without any medical intervention.

14. History of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, Stevens Johnsons syndrome (SJS), or hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any other excipient present in the pharmaceutical form of the investigational medicinal product(s).
15. History of second malignancy within 3 years prior to study treatment except for curatively treated cervical cancer *in situ*, non-melanoma skin cancer, or superficial bladder cancer.

5. TREATMENT

5.1. Investigational Product

See Study Protocol DAY101-102 (Master Protocol).

5.2. DAY101 Administration

5.2.1. General Dosing Instructions

Dosing for an individual should be at a consistent day and time (± 12 hours) each week. There is no restriction with regard to intake of food (patients can be fed or fasted). Tablets should not be cut or crushed.

If the patient vomits the tablets and they are still recognizable, then the patient can be re-dosed. If the patient vomits within 30 minutes of ingesting tablets and the tablets are not recognizable, the patient or parent/legal guardian should be instructed to call the Investigator or study nurse to discuss whether the patient should take any additional tablets. If it has been longer than 30 minutes or the Investigator or study nurse is not reachable, the patient should not be re-dosed.

The patient or the patient's parent/legal guardian will complete a study drug administration diary to record dosing compliance. The study drug administration diary will be reviewed at each clinic visit by the Investigator or study staff. The study drug administration diary will also be assessed at each clinic visit.

Late doses (i.e., between 12 and 72 hours of regularly scheduled dose) should be noted in the diary. Doses that are late by more than 72 hours (3 days) should be skipped and recorded in the dosing diary as missed. A minimum of 4 days should occur between doses. Any dose that cannot be given within 3 days of the scheduled dose should be recorded as missed.

For adolescent patients, dose rounding guidelines by body surface area (BSA) are provided in Table 3. Any questions regarding dose rounding should be directed to the Sponsor Medical Monitor. BSA should be calculated and an updated dose should be provided on Day 1 of each cycle (See Appendix J of Master Protocol DAY101-102).

Table 3: Dose Rounding Guidelines in Adolescents with BSA 0.9 ->1.4 m^2 for DAY101 420 mg/m^2 QW

BSA (m^2)	420 mg/m^2 (mg)
[redacted]	
[redacted]	
[redacted]	

Abbreviations: BSA, body surface area; QW, every week.

5.2.2. Dose-Limiting Toxicity

Not applicable.

5.2.3. Dose Modifications

Patients who experience a treatment-emergent adverse event (TEAE) that is clinically or medically intolerable, such as peripheral/facial/periorbital edema, hematotoxicity, hyperbilirubinemia, or cardiac, pulmonary, or renal toxicity, should have DAY101 dosing interrupted until adverse events (AEs) are resolved to Grade 1 or baseline level. Patients should be reevaluated at least weekly for resolution of the AE. Upon resolution, dosing may be restarted at the original dose of DAY101 if toxicity resolves in 2 weeks. Otherwise consider dose reduction(s) as shown in Table 4.

For patients who experience a TEAE that is clinically or medically intolerable more than once, a second dose reduction may be considered as shown in Table 4.

For specific instructions on dose reduction for ocular disturbances, rashes, photosensitivity, increased creatine phosphokinase (CPK), increased liver transaminases, and QTc prolongation please see dose modification recommendations in Section 5.2.4 .

All patients who experience drug-related toxicity requiring a recovery period longer than 28 days will be withdrawn from study drug administration unless there is evidence of benefit and no alternative treatment available as determined by the Investigator and approved by the Sponsor.

Table 4: Dose Level Reductions for DAY101 Based on Recommend Phase 2 Dose for Weekly Regimen in Adult and Adolescent Patients

Patient Age	Starting Dose	First Dose Reduction [a] (reduce or discontinue dose)	Second Dose Reduction [a] (reduce or discontinue dose)
≥ 18 years	600 mg QW	500 mg QW	400 mg QW
≥ 12 up to <18 years	420 mg/m^2 QW	350 mg/m^2 QW	280 mg/m^2 QW

Abbreviations: eCRF, electronic case report form; QW, every week.
[a] All dose reductions must be recorded on the eCRF.

5.2.4. Management of Treatment-Related Events

Included below are toxicity management guidelines.

5.2.4.1. Ocular Disturbances

Patients must be instructed to report visual symptoms as soon as they occur. An eye examination will be performed by an ophthalmologist or other qualified site clinical personnel while on study and at any time visual abnormalities are described by the patient. Regular monitoring and management of visual symptoms may avoid more serious ocular complications.

Retinal Detachment

Ocular toxicities are graded according to Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0 and follow those definitions. Retinal detachment is commonly graded in two ways. Rhegmatagenous retinal detachment (RDD) refers to a tear in the retina most

commonly due to trauma or age-related vitreous retraction. In contrast, serous retinopathy (SR) results in retinal detachment through the buildup of fluid behind the retinal layer. Serous retinopathy (SR), serous retinal detachment (SRD), and retinal pigment epithelium disorder (RPED), all refer to the same process and are graded in CTCAE v5 under Retinopathy (Grade 1–4). If SR/SRD/RPED are diagnosed, monitor, and manage under the care of the clinical expert (e.g., ophthalmologist) according to Table 5 If symptoms do not resolve within 4 weeks after DAY101 is held, discontinue treatment with DAY101.

Table 5: Serous Retinopathy (SR)/Serous Retinal Detachment (SRD)/Retinal Pigment Epithelium Disorder (RPED) Management Recommendations

AE Grade	Event Description	Recommendation
Grade 1	Asymptomatic; clinical or diagnostic observations only	Monitor closely with weekly ophthalmologic examinations. No change in DAY101 dose or schedule.
Grade 2	Mildly symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Monitor closely with weekly ophthalmologic examinations. Hold DAY101 if symptoms do not improve in 2 weeks. If resolution in ≤ 2 weeks, resume DAY101 at same dose. Otherwise, consider a dose reduction (see Table 4).
Grade 3	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL	Monitor closely with weekly ophthalmologic examinations. Hold DAY101 until signs and symptoms improve to baseline or Grade 1. Resume at the same dose if symptoms resolve within 2 weeks. Otherwise, consider a dose reduction (see Table 4).
Grade 4	Best corrected visual acuity of 20/200 or worse in the affected eye	Monitor closely with weekly ophthalmologic examinations. Hold DAY101 until signs and symptoms and visual acuity tests improve to baseline or Grade 1. Resume at the same dose if symptoms and visual acuity tests resolve within 2 weeks. Otherwise, discuss the doses of DAY101 with Sponsor prior to resuming treatment.

Abbreviations: ADL, activities of daily living
Source: Van Rijssen 2019 et. al.

Rhegmatagenous Retinal Detachment (RDD)

If Grade 3 or 4 RDD occurs and surgical treatment is required, immediately discontinue treatment with DAY101. Appropriate follow-up and treatment measures must be taken by the treating ophthalmologist. The Sponsor must be notified immediately.

Retinal Vein Occlusion

If retinal vein occlusion (RVO) is diagnosed, immediately discontinue treatment with DAY101. Appropriate follow-up and treatment measures must be taken by the treating ophthalmologist or other qualified site clinical personnel. The Sponsor must be notified immediately.

5.2.4.2. Dermatologic Toxicity

Rashes (maculopapular and dermatitis acneiform) have been observed with DAY101 administration. Patients should be advised to contact the Investigator immediately if they develop a new rash or have worsening of an existing rash while on the study. Patients should be referred to a dermatology department when symptoms are impairing function (e.g., cannot sleep, sit still) or psychosocially bothersome, and when management techniques fail to resolve.

See Appendix C for recommended prophylactic skin care regimen and management options for rashes. It is recommended all patients receiving DAY101 follow the prophylactic skin care regimen. Rash management recommendations should be followed as outlined in Table 6.

Table 6: Rash Management Recommendations

AE Grade	Event Description	Recommendation
Grade 1	Papules and/or pustules covering < 10% BSA	Initiate oral antihistamines or topical steroids. No change in DAY101 dose or schedule.
Grade 2	Papules and/or pustules covering 10–30% BSA	In addition to topical antihistamines and steroids, treatment with minocycline or topical clindamycin should be considered.
Grade 3	Papules and/or pustules covering > 30% BSA with moderate or severe symptoms; limiting selfcare ADL; associated with local superinfection with oral antibiotics indicated	Initiate appropriate treatment for associated infection in consultation with dermatologist or specialist. DAY101 should be held or dose reduced until AE resolved to Grade 1 or returns to baseline. DAY101 may be resumed at original dose if the symptoms improve within 2 weeks or consider dose reduction (see Table 4). If a Grade 3 skin toxicity recurs at a reduced dose, a second dose reduction may be considered. If a Grade 4 rash recurs at a reduced dose, discontinuation of treatment is required.
Grade 4	Life-threatening; papules and/or pustules covering any %BSA; extensive superinfection with IV antibiotics indicated	

Abbreviations: ADL, activities of daily living; AE, adverse event; BSA, body surface area; IV, intravenous.
Source: Lemech 2012 et. al.

Permanent discontinuation of study therapy is recommended in case a patient develops unexpected severe dermatologic AEs such as Stevens Johnson syndrome or toxic epidermal necrolysis. Additionally, permanent discontinuation of study therapy is recommended for patients with treatment-related skin rash associated with Grade 3 systemic organ dysfunction

(cardiac, hepatic, pulmonary, renal, or lymphadenopathy) possibly indicating a drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.

5.2.4.3. Photosensitivity

Photosensitivity is a recognized class effect of RAF kinase inhibitors. For background information on phototoxicity in DAY101, refer to the current version of the investigator's brochure (IB). Patients should avoid excess exposure to sunlight and ultraviolet (UV) light and use sunglasses and broad-spectrum, skin-sensitive formulation sunscreen (eg, containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥ 50. Patients should be instructed to monitor for signs and symptoms of photosensitivity (eg, itchy eruptions or areas of redness and inflammation on patches of sun-exposed skin).

5.2.4.4. Increased Creatine Phosphokinase

Consider alternative causes for increased CPK such as increased physical activity, trauma/ falls, muscle injury, and other causes (e.g., statins, alcohol, toxins, heat illness, seizure). Test for blood urea nitrogen (BUN), creatinine, urinalysis with myoglobin test, troponin I or troponin T as clinically indicated.

See recommendations in Table 7 following an increase in CPK during the study.

Table 7: Increased Creatine Phosphokinase Management Recommendations

AE Grade	Event Definition	Recommendation
Grade 1	> ULN – 2.5 × ULN	• Monitor closely • Adequate hydration is recommended to maintain fluid and electrolyte balance and tissue perfusion
Grade 2	> 2.5 × ULN – 5 × ULN	
Grade 3/ Grade 4	> 5 × ULN – 10 × ULN > 10 × ULN	• Manage symptomatically • Hold DAY101, if clinically symptomatic • Resume DAY101 at original dose if symptoms return to Grade 1 or baseline within 2 weeks. Otherwise, reduce DAY101 dose (see Table 4). If an asymptomatic Grade 3 or 4 CPK elevation occurs at a reduced dose, a second dose reduction may be considered. If the second occurrence of Grade 3 or 4 CPK elevation is symptomatic, discontinuation of treatment is required.

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; ULN, upper limit of normal.
Source: Common Terminology Criteria for Adverse Events, version 5.0.

5.2.4.5. Increased Liver Transaminases and Bilirubin

Mild to severe increases in serum transaminases (ALT and AST) and bilirubin have been observed in patients treated with DAY101.

Should an increase in AST/ALT and/or bilirubin be observed while receiving DAY101, the recommendations from Table 8 should be followed.

Table 8: Increased Liver Transaminases and Bilirubin Recommendations

AE Grade	Event Definition	Recommendation
Grade 1/Grade 2	Asymptomatic, absolute increase in AST or ALT to < 5 × ULN or to < 5 × increase from baseline or bilirubin ≤ 3 × ULN or to ≤ 3 × increase from baseline	• No change in DAY101 dose.
≥ Grade 3	Absolute increase in AST or ALT to ≥ 5 x ULN or > 5 × increase from baseline or bilirubin > 3 × ULN or > 3 × increase from baseline	• Withhold DAY101 until AST/ALT/or bilirubin abnormality resolved to < Grade 3 AND baseline level. • Resume DAY101 at original dose if the AST, ALT, or bilirubin abnormality resolves within 8 days. • Patients whose resolution of AST, ALT, or bilirubin abnormality is taking longer than 8 days may have their DAY101 dose reduced (see Table 4). • If a Grade 3 or 4 LFT or bilirubin elevation recurs at a reduced dose, a second dose reduction may be considered if asymptomatic and isolated (i.e., not associated with an increase in bilirubin).

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; ULN, upper limit of normal

5.2.4.6. QTc Prolongation

Prior to concluding that an episode of prolongation of the QTc interval is due to study drug, thorough consideration should be given to potential precipitating factors (e.g., change in the patient's clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist. See Table 9 for QTc prolongation recommendations.

Table 9: QTc Prolongation Recommendations

QTc Interval	Recommendation
> 500 msec (> 18 years) > 480 msec (< 18 years)	• ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate • If manual reading verifies a mean QTc interval of > 500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia, and concomitant medications for drugs with the potential to prolong the QTc interval [Appendix B]) should be performed • Repeat ECGs should be performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to < 500 msec, and the judgment of the Investigator(s) and Sponsor is determined to be due to cause(s) other than study drug, treatment may be continued with regular ECG monitoring. – If, in that timeframe, the QTc intervals rise above 500 msec, the study drug will be held until the QTc interval decreases to < 500 msec. Patients will then re-start the study drug at the next lowest dose level. – If the QTc interval has still not decreased to < 500 msec after 2 weeks, or if at any time a patient has a prolonged QTc and becomes symptomatic, the patient will be removed from the study.

Abbreviations: ECG, electrocardiogram.

5.3. Removal of Patients from Therapy or Assessment

See Study Protocol DAY101-102 (Master Protocol).

5.4. Prior and Concomitant Medications

5.4.1. General

All medications that were used from 28 days prior to enrollment through 30 days following the last dose of study drug will be recorded in the electronic case report form (eCRF). All prior anticancer treatments, regardless of when they were administered, will also be collected. These are to include prescription medications and transfusions. Excluded prior medications are those excluded via the eligibility criteria.

5.4.2. Allowed Concomitant Medications

The Investigator should instruct the patient or the patient's parent or legal guardian to notify the study site about any new medications he/she takes after starting study drug.

Patients taking medication chronically should be maintained on the same dose and schedule throughout the study period, as medically feasible.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is permitted, except as specifically prohibited in Section 5.4.3. Medications required to treat AEs and manage cancer symptoms and concurrent stable diseases, and supportive care agents, such as pain medications, antiemetics, short courses of steroids, and antidiarrheals, are allowed. Oral contraceptive pills are permitted. Cannabis use, including cannabidiol (CBD) and topical tetrahydrocannabinol (THC) products, are not prohibited during the course of the study, as the risk of a drug-drug interaction with DAY101 is assessed as low.

As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored, as potential drug-drug interactions between DAY101 and other drugs have not been studied in humans.

Medications known to cause hypo- or hypermagnesemia and hypophosphatemia should be used with caution.

Additionally, medications known to cause QTc prolongation should be used with caution (refer to Appendix B).

Patients should also be instructed to consult with the Investigator before taking any new medications, including over-the-counter products.

Routine vaccinations should be administered per local institutional guidelines.

5.4.3. Prohibited Concomitant Medications

As DAY101 is a substrate of CYP2C8, patients should avoid strong inhibitors or inducers of CYP2C8 (refer to Appendix A), as they could alter the drug's PK. Medications that are substrates of BCRP with a narrow therapeutic index are prohibited during this study. During this study, patients are not allowed to receive other chemotherapeutic agents (traditional chemotherapy, targeted agents, monoclonal antibodies, etc.), drugs with immunosuppressant properties (other than steroids as allowed per Section 5.4.2), or any other investigational agents besides DAY101.

5.4.4. Palliative Radiotherapy

In general, measurable lesions being used to measure response should not be irradiated without discussion with the Sponsor and may be reason for the patient to be removed from study for progressive disease. Irradiated non-measurable lesions will be considered not evaluable for response, but still can be used to assess progressive disease. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate eCRF.

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician after discussion and approval by the Sponsor. DAY101 must be held for 6 days before beginning radiation therapy and patients are permitted to restart DAY101 6 days following completion of radiation therapy.

6. TESTS AND EVALUATIONS

6.1. Screening

See Study Protocol DAY101-102 (Master Protocol).

6.2. Enrollment

See Study Protocol DAY101-102 (Master Protocol).

6.3. Medical History and Malignancy History

See Study Protocol DAY101-102 (Master Protocol).

6.4. Archival Tumor Samples

Archival tumor tissue may come from a specimen obtained at either diagnosis or recurrence (preferably less than 3 years old). If an archival tumor tissue sample is not available, a freshly acquired tumor sample or liquid biopsy obtained at baseline to confirm presence of MAPK alteration is required. Tumor samples may be either formalin-fixed, paraffin-embedded (FFPE) tissue, freshly cut FFPE slides, snap frozen tissue, or a liquid biopsy processed and shipped to the Central Lab as per the Laboratory Manual.

Note: If archival tissue is unavailable, freshly acquired tumor tissue or liquid biopsy is required.

Please refer to Section 6.4 for additional freshly acquired tissue requirements.

6.5. Freshly Acquired Tumor Samples for Pharmacodynamic Analysis

Freshly acquired tumor tissue samples are to be collected for pharmacodynamic analysis at pre- and on-treatment timepoints as per the Schedule of Activities for all patients where safe to obtain as determined by the Investigators. Tumor samples must be collected after drug dosing for that day, except for [redacted] in which collection must be pre-dose. Tumor samples must be processed and shipped to the Central Lab as per the Laboratory Manual.

6.6. ctDNA Samples: Blood

See ctDNA blood samples will be collected during [redacted]. See laboratory manual for ctDNA sample collection regimen.

6.7. Physical Examination

See Study Protocol DAY101-102 (Master Protocol).

6.8. Eastern Cooperative Oncology Group (ECOG) /Lansky Performance Status

See Study Protocol DAY101-102 (Master Protocol).

6.9. Assessment of Change in Pubertal Development (Tanner Stage)

See Study Protocol DAY101-102 (Master Protocol).

6.10. Vital Signs

See Study Protocol DAY101-102 (Master Protocol).

6.11. Ophthalmology Examination (All Patients)

A baseline eye examination will be performed by an ophthalmologist or a qualified site clinical personnel. Consultation with an ophthalmologist or a qualified site clinical personnel is required if abnormal ocular AEs arise as specified in Section 5.2.4.1.

The following assessments should be completed at screening:

Fundus examination with comment on retinal abnormalities

Best corrected visual acuity (BCVA)

6.12. Visual Symptom Assessment

Patients must be asked at each time point if they have any changes in vision. If the patient has noted any visual changes, an eye examination must be performed by an ophthalmologist or a qualified site clinical personnel prior to further dosing of DAY101 or combination partner.

6.13. Dermatologic Examination

See Study Protocol DAY101-102 (Master Protocol).

6.14. Neurologic Examination

See Study Protocol DAY101-102 (Master Protocol).

6.15. Height and Bone Age

See Study Protocol DAY101-102 (Master Protocol).

6.16. Cardiac Function

6.16.1. Electrocardiograms

See Study Protocol DAY101-102 (Master Protocol).

6.16.2. Echocardiogram/Multiple-Gated Acquisition

See Study Protocol DAY101-102 (Master Protocol).

6.17. Laboratory Tests

For pediatric patients (aged < 18 years), blood volumes drawn will be minimized, in accordance with the European Commission (EC)'s recommendations, "Ethical considerations for clinical trials on medicinal products conducted with the pediatric population" (2008) and "Ethical considerations for clinical trials on medicinal products conducted with minors" (2017).

See Study Protocol DAY101-102 (Master Protocol).

6.17.1. Pregnancy Test

See Study Protocol DAY101-102 (Master Protocol).

6.17.2. Hematology

See Study Protocol DAY101-102 (Master Protocol).

6.17.3. Serum Chemistries

See Study Protocol DAY101-102 (Master Protocol).

6.17.4. Coagulation Panel

See Study Protocol DAY101-102 (Master Protocol).

6.17.5. Thyroid Function Tests

See Study Protocol DAY101-102 (Master Protocol).

6.18. Pharmacokinetic Samples: Blood

The dose of DAY101 should be taken in the clinic on pharmacokinetic (PK) sampling days to ensure that a PK sample is collected as scheduled related to the time of dosing. PK samples will be collected and handled as outlined in the Laboratory Manual.

The blood sampling regimens for determining the PK of DAY101 is shown in Table 10. Blood samples for DAY101 concentration measurements will be collected on all patients in the study. Exact dates and clock times of drug administration and actual PK blood draw should be recorded on the appropriate eCRF.

If a patient experiences an AE that fits the criteria of a serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR) as determined by the Investigator, a blood sample should be collected, whenever possible, for measurement of drug concentrations at or around that time.

When a blood sample is taken on the same day as an ECG assessment, the ECG should be performed prior to sample collection (within 15 minutes prior). When a blood sample is taken on the same day as a vital signs assessment, the vital signs should be collected prior to sample collection.

Table 10: Schedule of Blood Sample Collections for DAY101 Pharmacokinetics

Cycle	Day	Pharmacokinetics Timepoint
	[redacted]	

6.19. Disease Assessment

6.19.1. Tumor Measurements

See Study Protocol DAY101-102 (Master Protocol).

6.19.1.1. Collection of Radiographic Studies for Independent Review

See Study Protocol DAY101-102 (Master Protocol).

6.20. Telephone/Telemedicine Visit

See Study Protocol DAY101-102 (Master Protocol).

6.21. Survival Status

See Study Protocol DAY101-102 (Master Protocol).

6.22. Study Drug Administration and Dosing Diary

See Study Protocol DAY101-102 (Master Protocol).

6.23. Concomitant Medication

See Study Protocol DAY101-102 (Master Protocol).

6.24. End of Treatment Visit

See Study Protocol DAY101-102 (Master Protocol).

6.25. Safety Follow-up Visit

See Study Protocol DAY101-102 (Master Protocol).

6.26. Long-Term Follow-up

See Study Protocol DAY101-102 (Master Protocol).

6.27. Force Majeure Flexibility

See Study Protocol DAY101-102 (Master Protocol).

7. PLANNED ANALYSES

See Study Protocol DAY101-102 (Master Protocol).

7.1. Analysis Populations

See Study Protocol DAY101-102 (Master Protocol).

7.2. Determination of Sample Size

For Study DAY101-102a, Simon's 2-stage design (Simon 1989) will be used to determine whether DAY101 has sufficient anticancer activity to warrant further development for each biomarker selected cohort. Enrollment per cohort may be terminated early independently of each other. No adjustment for multiple hypothesis testing will be made if both cohorts complete enrollment.

The Sponsor may consider replacing the patient if the patient is not considered evaluable for response assessment in the Simon stage 1. The stage 2 will not be activated if the stage 1 minimum number of responses (as shown in table below) is not met and all patients have been followed for at least 6 months.

Specific performance criteria are presented in Table 11.

Table 11: Sample Size Determinations

	Null/Alternative Hypotheses	Study Power	Study Alpha (1-sided)	Stage 1 n (Minimum Number of Responses to Move to Stage 2)
Melanoma cohort	[redacted]			
Tissue agnostic cohort	[redacted]			

7.3. Statistical Methods

See Study Protocol DAY101-102 (Master Protocol).

7.3.1. Efficacy Analyses

See Study Protocol DAY101-102 (Master Protocol).

7.3.2. Safety Analyses

See Study Protocol DAY101-102 (Master Protocol).

7.3.3. Pharmacokinetic Analyses

Plasma concentrations of DAY101 will be analyzed at specified time points using validated bioanalytical method. Plasma concentrations will be summarized by nominal sample time using standard summary statistics for PK concentrations.

8. ADVERSE EVENTS

See Study Protocol DAY101-102 (Master Protocol).

8.1. Stopping Rules

See Study Protocol DAY101-102 (Master Protocol) Section 8.3 for details regarding stopping rules.

8.2. Independent Data Monitoring Committee

See Study Protocol DAY101-102 (Master Protocol) Section 8.2 for details regarding the independent data monitoring committee (DMC).

8.2.1. Risk Management

See Study Protocol DAY101-102 (Master Protocol).

8.2.2. Continuous Review of Safety Data

See Study Protocol DAY101-102 (Master Protocol).

9. STUDY ADMINISTRATION

See Study Protocol DAY101-102 (Master Protocol).

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Appendix A: List of Medications with Potential Drug Interactions with DAY101

Table 12: List of Medications with Potential Drug Interactions with DAY101

CYP2C8 Inducers	CYP2C8 Inhibitors
rifampin	gemfibrozil clopidogrel
BCRP substrates with narrow therapeutic index	
Methotrexate, topotecan, or irinotecan	

Abbreviations: BCRP=breast cancer resistance protein; CYP =cytochrome P450
Note: The above lists are not exhaustive. See also: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Appendix B: List of Medications Known to Cause QTc Prolongation

Table 13: Drugs Associated with QTc Prolongation and Torsades de Pointes

Antiarrhythmics	Antimicrobials	Antidepressants	Antipsychotics	Others
Amiodarone	Levofloxacin	Amitriptyline	Haloperidol	Cisapride
Sotalol	Ciprofloxacin	Desipramine	Droperidol	Sumatriptan
Quinidine	Gatifloxacin	Imipramine	Quetiapine	Zolmitriptan
Procainamide	Moxifloxacin	Doxepin	Thioridazine	Arsenic
Dofetilide	Clarithromycin	Fluoxetine	Ziprasidone	Dolasetron
Ibutilide	Erythromycin	Sertraline		Methadone
	Ketoconazole	Venlafaxine		
	Itraconazole			

Source: U.S. Pharmacist [Internet]. Jobson Publishing Corp. c2000-2022 [cited 2022 Feb 23]. Available from: https://www.uspharmacist.com/article/drug-induced-qt-prolongation

Appendix C: Rash Prophylaxis and Management

Recommended Preventative Skin Care Routine

Rash Prophylaxis and Management

A baseline dermatological exam should be performed by the Investigator and/or a dermatologist. Subsequent examinations should be symptom-directed, as clinically indicated.

Patients should be referred to a dermatologist when (1) symptoms are impairing function (e.g., cannot sleep or sit still) or (2) psychosocially bothersome, and when the below management techniques fail to resolve.

Recommended Preventative Skin Care Routine for All Patients

Patients should perform regular preventative skin care routine that includes the following:

Sun Protection Measures

1. Avoid excess exposure to sunlight and UV light
2. Use SPF ≥ 50 sunscreen and reapply every 2 hours or as needed
3. Wear sun-protective clothing
4. Limit sun exposure during peak hours of 10AM to 4PM

Gentle Skin Care

1. Take daily lukewarm baths or showers
2. Use unscented, gentle cleansers
3. Apply skin-sensitive moisturizer daily after bath or shower
4. Take diluted skin baths or diluted bleach baths every other day (3 to 4 times per week)

Bleach Bath Instructions

Diluted skin baths or diluted bleach baths may help reduce the risk of infection and ameliorate inflammation and pruritus

1. One quarter-cup to one-half cup of bleach is added to a full bathtub, or 1 teaspoon per gallon.
2. The patient soaks for 5-10 minutes, followed by a rinse with water and application of an emollient diffusely on the skin.