CLINICAL MASTER PROTOCOL DAY101-102

A Phase 1b/2, Open Label Study of DAY101 Monotherapy or Combination with Other Therapies for Patients with Recurrent, Progressive, or Refractory Solid Tumors Harboring MAPK Pathway Aberrations

Investigational Product:	DAY101
Protocol Number:	DAY101-102
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Development Phase:	1b/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	13 October 2022

Protocol Approval Page

Protocol Title:	A Phase 1b/2, Open Label Study of DAY101 Monotherapy or Combination with Other Therapies for Patients with Recurrent, Progressive, or Refractory Solid Tumors Harboring MAPK Pathway Aberrations
Protocol Number:	DAY101-102
Protocol Amendment 2.0	13 October 2022

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

[redacted]

[redacted]
Date

I have carefully read Protocol DAY101-102 entitled "A Phase 1b/2, Open Label Study of DAY101 Monotherapy or Combination with Other Therapies for Patients with Recurrent, Progressive, or Refractory Solid Tumors Harboring 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

Master Protocol DAY101-102 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, 2	Revised Phase 1b/2 exploratory objective.	Revised to reflect genomic alterations in circulating tumor DNA (ctDNA) will be characterized.
Synopsis, 4.1, 4.2	Moved all eligibility criteria into sub-protocols.	Restructured eligibility criteria between DAY101-102 and sub-protocols.
1.2.1	Revised languages on metabolic pathway and conclusions for drug-drug interaction potentials.	Provided clarity on DAY101 drug-drug interaction potentials with concomitant drugs.
1.2.2, 1.3.2	Added description for Study [redacted] Study [redacted] and FIREFLY-1/PNOC026.	Provided a concise summary of safety data for Study [redacted] and data on the PK profile of DAY101 tablet and powder for reconstitution (PfR) formulations for Study [redacted]
1.2.2.2, 1.2.2.3	Added clinical efficacy and safety data from Study FIREFLY-1/PNOC026. A table of TEAEs was added from completed Study C28001. Revised data from Study [redacted]	To add findings as of the data cutoff of 14 April 2022 and to provide additional background on the safety data.
1.3.1	Removed mention of Harvey Rat Sarcoma Virus (HRAS) mutation.	HRAS mutation is not mentioned in referenced sub-protocol.
1.3.2	Updated the justification for dose. Revised data from Study [redacted] Provided a concise summary of data on the pharmacokinetic (PK) profile of DAY101 tablet formulation. Revised data from Study [redacted]	Revised results from Study [redacted]. Provided a concise summary of data on the PK profile of DAY101 tablet and PfR formulations.
1.3.3	Updated section and guidance regarding CYP2C8 inhibitors or inducers.	Based on updated available information.
1.3.4	Updated Benefit/Risk description.	Updated based on updated available clinical data.

Section(s)	Description of Change	Brief Rationale
2 (Table 2)	Removed duplicate secondary objective.	Revised per protocol clarification letter-Canada recommendations. ORR is erroneously listed as a secondary endpoint whereas it serves as a primary endpoint only for the Phase 2 portion of the study.
3.1	Added "and combination partner if applicable" with regards to continuing with drug if patient has radiographic evidence of disease progression.	Revised for consistency with sub-protocol DAY101-102b.
3.1	Revised schema.	Removed indication expansion and updated schema for clarity.
3.1	Removed body surface area (BSA) parameter for patients ages 12 up to <18 years.	BSA $\geq$ 1.5 m^2 for patients 12 up to < 18 years is not an eligibility criterion.
5.1	Removed dispensing instructions.	Details to be provided in the Pharmacy Manual.
5.2.1	Clarified dosing instructions.	General dosing instructions revised to align with DAY101 programs.
5.2.3, 5.2.4	Removed dose modification and management of treatment-related event details.	Details can be found in respective sub-protocols.
5.4.4	Clarified window for recording medications in electronic case report form.	Revised to align between studies.
5.4.5	Removed palliative radiotherapy details.	Relocated details to respective sub-protocols.
5.5	Added preparation, handling, storage, and accountability for study drug.	To provide guidance and clarify medication handling.
6.2	Removed statement that patients that are lost to follow up will be replaced.	Updated enrollment procedure
6.4	Removed archival and tumor sample details.	Relocated details to respective sub-protocols.
6.5	Added section for fresh tumor samples for pharmacodynamic analysis.	Clarity to site and investigator.
6.7	Added section for ctDNA blood sample collection.	Clarity to site and investigator.
6.9	Added Tanner Staging for assessment of pubertal development.	Clarity to site and investigator.
6.9, Appendix H	Removed routes of obtaining body temperature. Addition of oxygen saturation assessment to vital signs	Per French National Agency for the Safety of Medicines and Health Products (ANSM) request, added oxygen saturation for monitoring of pulmonary toxicities.
6.10	Clarified blood pressure assessment in pediatric patients.	Clarity to site and investigator.

Section(s)	Description of Change	Brief Rationale
6.13	Added recommendation for prophylactic skin care regimen and management options.	Clarity to site and investigator.
6.15	Added bone age and height assessment.	For additional collection of data.
6.17	Added guidance regarding laboratory tests for patients ages 12 up to <18 years.	Clarity to site and investigator.
6.17.2	Removed neutrophil (count and percentage) and lymphocytes.	Removed the specification since already included with current assessment.
6.17.3	Addition of the following chemistry assessments: serum calcium (corrected calcium), creatinine clearance, phosphate, and magnesium.	Per Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) request, additional assessments added to monitoring parameters.
6.17.5	Clarified triiodothyronine (T3) testing.	To clarify T3 may be obtained as a reflexive test if considered necessary by the Investigator based on local practice.
6.19.1	Added that CT/MRI must be performed within 28 days prior to first dose of study drug.	Clarity to site and investigator.
6.20	Removed 7-day monitoring period.	Details specified in sub-protocols.
6.25	Removed timeframes for AE reporting.	To reduce discrepancies.
7	Removed details.	Details can be found in sub-protocols and SAP.
7.1	Revised analysis population.	To clarify efficacy population.
7.3.1	Revised efficacy analyses.	To align with efficacy population description.
7.3.2	Revised safety analyses.	To clarify how information will be tabulated and included in summary tables and listings for all reported TEAEs.
7.3.2.2	Added descriptive statistic language.	To clarify descriptive statistics used for clinical laboratory parameters.
8, Appendix G	Added adverse events of special interest guidance.	To clarify that safety monitoring includes all AESIs.
8.1.4	Updated regulatory reporting requirements to clarify SAE and AESI reporting.	Clarity to site and investigator.
8.1.5	Clarified reporting is for DAY101 or combination partner, whichever administered last.	To clarify reporting window.
8.2; 8.2.1; 8.2.2	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 an IDMC for analysis of cumulative safety data throughout study conduct.

Section(s)	Description of Change	Brief Rationale
9.2	Removed eCRF window.	To reduce redundancy. Information is in the electronic data capture manual.
10	Added new citations.	Updated to reflect current version of protocol.
Appendix F	Revised contraceptive guidance.	Contraceptive guidance information has been revised to align with DAY101 programs.

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 1b/2, Open Label Study of DAY101 Monotherapy or Combination with Other Therapies for Patients with Recurrent, Progressive, or Refractory Solid Tumors Harboring MAPK Pathway Aberrations.

STUDY SITES:

See sub-protocol for details.

PHASE:

1b/2

OBJECTIVES:

The Phase 1b objectives will only apply to sub-protocol of DAY101 in combination with other therapies.

Phase 1b

The Phase 1b objectives will apply to the investigation of DAY101 in combination with other therapies. Additional objectives may be specified according to the related sub-protocol.

Primary Objective:

- To determine the safety of DAY101 in combination with other therapies.
- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of DAY101 in combination with other therapies.

Secondary Objectives:

- To assess the efficacy of DAY101 in combination with other therapies by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or appropriate tumor response criteria.
- To characterize the pharmacokinetic (PK) profile of DAY101 in combination with other therapies.
- To characterize pharmacodynamic (PD) effects of DAY101 in combination with other therapies.

Exploratory Objectives:

- To evaluate the genomic profile of archival tumor biopsies or fresh tumor biopsies (if available) and circulating tumor DNA (ctDNA) from patients who will be treated with DAY101 in combination with other therapies.
- To characterize pathway modulation and/or genomic alterations in tumor biopsies.
- To characterize genomic alterations in ctDNA.
- [redacted]

Phase 2

The Phase 2 objectives will apply to the investigation of DAY101 as monotherapy and in combination with other therapies. Additional objectives may be specified according to the relevant sub-protocol.

Primary Objective:

To evaluate the efficacy of DAY101 by RECIST version 1.1 or appropriate tumor response criteria as a monotherapy or in combination with other therapies

Secondary Objectives:

- To assess the safety and tolerability of DAY101 as monotherapy or in combination with other therapies.
- To assess additional efficacy parameters of DAY101 as monotherapy or in combination with other therapies.
- To characterize the tumor responses observed with DAY101 as monotherapy or in combination with other targeted therapies.
- To characterize the PK profile of DAY101 in combination with other therapies
- To characterize the PD effects of DAY101 as monotherapy or in combination with other therapies.
- To determine the relationship between PK and PD of DAY101 in combination with other therapies.

Exploratory Objectives:

- [redacted]
- To evaluate the genomic profile of archival tumor or fresh tumor biopsies and ctDNA from patients who will be treated with DAY101 as monotherapy or in combination with other therapies.
- To characterize pathway modulation and/or genomic alterations from tumor biopsies.
- To characterize genomic alterations in ctDNA.
- [redacted]
- [redacted]

STUDY DESIGN:

This is a Phase 1b/2, multi-center, open-label, umbrella study of patients 12 years of age with recurrent or progressive solid tumors with alterations in the key proteins of the RAS/RAF/MEK/ERK pathway, which will be referred to as the mitogen-activated protein kinase (MAPK) pathway. 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.

Based on the identified alterations in the key proteins of the MAPK pathway, patients may be offered the opportunity to participate in one or more sub-protocols within this umbrella study of DAY101 as monotherapy or in combination with other therapies. Enrollment will be based on the specific eligibility criteria described in each sub-protocol.

Study DAY101-102 (master study) and sub-protocol consist of a screening period, a treatment period, a safety follow-up period, and a long-term follow-up period where survival, status and subsequent anticancer therapies are collected.

DAY101 will be administered as specified in the sub-protocol. Additional dose schedules may be explored. Dose level(s), dose schedule(s), and cycle lengths for DAY101 as monotherapy or in combination with other therapies will be specified in each sub-protocol. Cycles will repeat, as specified in each sub-protocol, until disease progression, unacceptable toxicity, or withdrawal of consent, or death. Patients will undergo radiographic evaluation of their disease at baseline, the end of [redacted] for 1 year and then [redacted] thereafter, or as specified in a given sub-protocol. Generally, response assessment will be performed according to 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.

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.

Scheduled activities will be outlined in the Schedule of Activities within each sub-protocol.

MAJOR ELIGIBILITY CRITERIA:

Eligibility criteria can be found within each sub-protocol.

PLANNED SAMPLE SIZE:

Total patients enrolled will depend on the sub-protocols included. For additional details, please see sub-protocols.

INVESTIGATIONAL DRUG:

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

Additional therapies may be included. For further details, please see relevant sub-protocols.

TREATMENT PROCEDURES:

For treatment procedures, please refer to relevant sub-protocol.

STUDY ASSESSMENTS:

Standard monitoring for safety is outlined in the protocol and sub-protocols and will include physical examination and anthropometric measurements, Eastern Cooperative Oncology Group (ECOG)/Lansky score, clinical adverse events, laboratory variables (e.g., hematology and serum chemistries), electrocardiogram (ECG), echocardiogram (ECHO)/multi-gated acquisition (MUGA), and vital signs.

Please see relevant sub-protocol for blood collection for PK assessments.

Please see relevant sub-protocols for radiology review procedures and tumor specimen collection procedures.

End of Study and Length of Study:

Please refer to relevant sub-protocol for information on duration of each study and end of study information.

STATISTICAL METHODS:

Sample Size Considerations:

Please see sub-protocols for sample size considerations relevant to each sub-protocol. Additional patients will be enrolled to account for any patients who are lost to follow-up or have no follow-up imaging.

Analysis Methods:

Efficacy Analyses

All efficacy analyses will be performed on the full analysis set (FAS) population, which includes all patients who received at least 1 dose of study drug and have measurable disease as determined by the Investigator at baseline and have at least 1 follow-up imaging or radiographically confirmed progressive disease prior to the first imaging timepoint as outlined in Section 7.3.1.

Overall response rate (ORR) as assessed by the proportion of patients with the best overall confirmed response of complete response (CR) or partial response (PR), according to the appropriate tumor response criteria as assessed by Investigator will be calculated and an exact confidence interval (CI) will be calculated. Duration of response (DOR) in patients with best overall response of CR or PR defined as from time of first tumor response to progression or date of data analysis, whichever occurs earlier as determined by the Investigator will be calculated. Progression free survival (PFS) is defined as the time from the date of the first dose of study drugs to the first occurrence of disease progression according to the appropriate tumor response criteria as assessed by Investigator, or death from any cause, whichever occurs earlier. Overall survival (OS) is defined as the period from the date of the first dose of study drugs until the date of death from any cause. Kaplan-Meier curves will be plotted for DOR, PFS, and OS. The timepoint for the analysis of response for Phase 2 studies' primary efficacy objective will be when all patients have a minimum of 6 months of follow-up.

Safety Analyses

Safety will be evaluated by monitoring all adverse events, serious adverse events, adverse events of special interest, and abnormalities identified through physical examinations, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). All verbatim adverse event terms occurring on or after first study treatment will be mapped to Medical Dictionary for Regulatory Activities (MedDRA), and adverse event severity will be graded according to NCI CTCAE v5.0.

Pharmacokinetic Analyses

Plasma concentrations of DAY101 and other therapies (as applicable based on sub-protocols) will be determined with validated bioanalytical methods. Plasma concentrations will be analyzed at specified time points in order to generate PK parameters as appropriate and will be described in more detail in the sub-protocol(s). Summary statistics will be generated as appropriate.

SCHEDULE OF ACTIVITIES

Scheduled activities will be performed in as outlined within each sub-protocol (see sub-protocol section, Schedule of Activities). Study procedures are included in this Master Protocol, Section 6.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve over the last 24-h dosing interval
AUC_{0-t}	area under the concentration-time curve from time zero to t
BBB	blood brain barrier
BCRP	breast cancer resistance protein
BCVA	best corrected visual acuity
BOR	best overall response
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
CL/F	apparent oral clearance of drug
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum drug concentration
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRAF	v-raf murine sarcoma viral oncogene homolog C
CRC	colorectal cancer
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CVA	cerebrovascular accident
CYP	cytochrome P450
D	Day
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DSMB	Data Safety Monitoring Board

Abbreviation or Term	Definition
EC	European Commission
ECG	electrocardiogram
eCRF	electronic case report form
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	End of Treatment
ERK	extracellular signal-related kinase
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIH	First-In-Human
FISH	fluorescence *in situ* hybridization
GCP	Good Clinical Practices
GDP	guanosine diphosphate
GTP	guanosine triphosphate
HGG	high-grade glioma
HREC	Human Research Ethics Board
IB	Investigator's Brochure
IC_{50}	inhibitory concentration equal to 50% maximal response
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio.
IRB	Institutional Review Board
IRC	independent review committee
IRT	interactive response technology
KRAS	Kirsten rat sarcoma viral oncogene homologue
LE	Long Evans
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
LGG	low-grade glioma
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Term	Definition
MEK	mitogen-activated protein kinase kinase
MRI	magnetic resonance imaging
mRNA	micro RNA
MTD	maximum tolerated dose
MUGA	Multiple-gated acquisition
NCI	National Cancer Institute
NRAS	neuroblastoma RAS viral oncogene homologue
NSCLC	non-small cell lung cancer
NTRK genes	neurotrophic tyrosine kinase receptor genes
OAT	organic anion transporter
OATP	organic anion transporting polypeptides
OCT	organic cation transporter
OPG	optic pathway glioma
ORR	overall response rate
OS	overall survival
PBPK	physiological based pharmacokinetic modeling and simulation
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
[redacted]	
PfR	powder-for-reconstitution
PFS	progression-free survival
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
pLGG	pediatric low-grade glioma
PO	*per os*, orally
PR	partial response
PTT	activated prothrombin time
[redacted]	
Q2D	every other day
QD	once-daily
QOL	quality of life
QT_c	QT interval corrected for heart rate
QT_cF	QT interval corrected for heart rate by Fridericia's formula
QW	once weekly
RAF	rapidly accelerated fibrosarcoma
RANO	Response Assessment in Neuro-Oncology
RAS	rat sarcoma virus

Abbreviation or Term	Definition
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RVO	retinal vein occlusion
SAP	statistical analysis plan
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	stable disease
SJS	Stevens Johnsons syndrome
T3	triiodothyronine
T4	tetraiodothyronine
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

DAY101 is an oral, selective, small-molecule, Type-II pan-rapidly accelerated fibrosarcoma (RAF) kinase inhibitor that is being developed by Day One Biopharmaceuticals, Inc. (Day One, the Sponsor) as monotherapy for the treatment of solid tumors with RAF fusions, RAF amplifications, and v-raf murine sarcoma viral oncogene homolog B (BRAF) mutations in adult and pediatric populations.

1.1. Background on Disease

1.1.1. Cancer Physiology

The mitogen-activated protein kinase (MAPK) signaling pathway is an essential pathway that regulates key cell functions, such as growth, survival, and differentiation. Genomic alterations and dysregulation of the MAPK pathway have been described in many different types of malignancies affecting adult and pediatric patients, including melanoma, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC) (Yaeger and Corcoran 2019). Across human tumors, rat sarcoma virus (RAS) mutations occur in 10–30%, BRAF in 6%, mitogen-activated protein kinase kinase (MEK) in < 1% of cases, and extracellular signal-related kinase (ERK) mutations are exceptionally rare (Yaeger and Corcoran 2019, Prior et al. 2020).

One of the most frequently altered genes in this pathway is *BRAF*, in which 90% of the mutations consist of the BRAF V600 point mutation (including amino acid substitutions V600E/K/D/R/M). This point mutation leads to both increased BRAF kinase activity that is independent of extracellular stimuli or RAS-guanosine triphosphate (GTP) and constitutive signaling that drives cell proliferation and tumor growth (Davies et al. 2002). Currently, the United States (US) Food and Drug Administration (FDA) has approved 3 agents that inhibit BRAF V600E/K: vemurafenib, dabrafenib, and encorafenib.

Beyond BRAF V600 point mutations, additional genomic alterations including non-V600 point mutations, BRAF fusions, and in-frame deletions have also been reported in human cancers (Ross et al. 2016). Non-V600 BRAF mutations can be found located in the activation segment, P-loop, catalytic loops, and DFG motif. BRAF fusions are rearrangements in which the N-terminal inhibitory domain of BRAF is replaced with a different sequence that enables BRAF to signal as a dimer independent of RAS activation. These alterations generally drive aberrant expression and constitutive activation of the kinase and downstream signaling pathway (Lu et al. 2017). Fusions involving oncogenes have historically been targetable by kinase inhibitors, and multiple targeted agents that have demonstrated clinical responses to cancer patients harboring fusions involving ABL, ALK, TRK, RET, and ROS1 have been approved by the US FDA and European Medicines Agency (EMA).

Beyond BRAF, other common genetic alterations can lead to the dysregulation of the MAPK pathway, such as RAS mutation. Oncogenic RAS mutations occur at hot spots that interfere with normal RAS regulation and function, such as the guanosine diphosphate (GDP)–GTP molecular switch, which leads to a constitutively active GTP-bound protein. Among RAS genes, Kirsten rat sarcoma viral oncogene homologue (KRAS) is most frequently mutated in cancer (85%), followed by NRAS (11%) and HRAS (5%) (Hobbs et al. 2016).

Targeting RAS has been challenging due to the difficulty in disrupting the protein:protein interactions that underlie its activation and function, although recent success has been observed with sotorasib (Lumakras™), an irreversible covalent inhibitor of KRAS G12C, in patients with advanced solid tumors harboring the KRAS G12C mutation (Mattingly et al. 2013, Hong et al. 2020). While sotorasib was recently approved for adult patients with NSCLC whose tumors harbor KRAS G12C, there is a need to develop KRAS inhibitors that impact beyond KRAS G12C mutation. Despite early success, early data with KRAS-G12C inhibitors have demonstrated mixed sensitivity of cell lines expressing KRAS G12C, with many cell lines able to sustain downstream RAS effector signaling with adaptive feedback through wild-type RAS proteins (Lito et al. 2016). For NRAS mutant tumors, single-agent MEK inhibitors such as binimetinib have been evaluated for the treatment of NRAS mutant melanoma in a Phase 3 study. Results of binimetinib versus dacarbazine in NRAS mutant melanoma have shown modest effect on tumor response (overall response rate [ORR] 15%) in NRAS mutant melanoma which did not translate into clinical benefit in overall survival (OS) (Dummer et al. 2017). Other treatments are being explored combining MEK inhibitors with other targets for both NRAS and HRAS positive cancers (Johnson and Puzanov, 2015, Boespflug et al. 2017, Scott et al. 2016). In summary, additional therapies or therapeutic approaches are needed to target tumors harboring mutations in RAS.

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 low-grade glioma and while, rare, these can also constitutively activate the MAPK pathway (Ryall et al. 2020, Williams et al. 2020). Thus, inhibition of CRAF/RAF1 could be a therapeutic strategy to target tumors harboring RAF 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 tumor cell lines are dependent upon *RAF1* activity for survival. Furthermore, bladder tumors with *HRAS* activating mutations are dependent on *RAF1*-mediated signaling and are sensitive to RAF1-targeted therapy, such as with a pan-RAF inhibitor. Together, these data identify *RAF1* and *HRAS* activation as a novel dependency in a subset comprising nearly 20% of urothelial tumors and suggest that targeting RAF1-mediated signaling represents a rational therapeutic strategy (Bekele et al. 2021).

1.1.2. Advanced Solid Tumors

Cancer is second leading cause of death in adults in the West (US, Europe) and the leading cause of death in the East (China, Japan, and Korea). In the United States in 2017, approximately 1 in 5 deaths are due to cancer. Although the overall 5-year survival rate for all cancers has been improving (67%, from SEER Cancer Stats, 2017), for those with advanced metastatic disease, their relative 5-year survival rates are poor, generally 30% or less. These data indicate that there is a great unmet need for additional anticancer agents with novel mechanisms of action.

1.1.3. Current Therapies

Treatment for advanced cancers is typically histology based and will vary across tumor types. They include most often combination chemotherapy and/or immunotherapy. Currently, the FDA and EMA have approved several agents specifically for the treatment of adults with BRAF V600E/K mutated melanoma, NSCLC, and CRC. They include Type-I BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) given alone or in combination with MEK inhibitors (cobimetinib, trametinib, binimetinib). These Type-I BRAF inhibitors exert their effect only on the BRAF V600 mutation. In the presence of wild-type BRAF, the mechanism of binding of these Type-I BRAF inhibitors is such that it results in the induced dimerization and paradoxical activation of wild-type RAF proteins in the presence of active RAS in non-tumor tissue. This leads to a common adverse event (AE) associated with these agents, the development of proliferative premalignant and malignant skin lesions (e.g., keratoacanthomas and squamous cell carcinomas). In addition, Type-I BRAF inhibitors are unable to effectively inhibit RAF dimers as formed by BRAF or CRAF fusions and are thus, unable to effectively inhibit the hyperactive ERK signaling that results from this fusion. In contrast to Type-I BRAF inhibitors, Type-II pan-RAF inhibitors, such as DAY101, inhibit both wild-type BRAF and CRAF/RAF1 and can inhibit both RAF monomers and dimers, avoiding the paradoxical activation observed with Type-I BRAF inhibitors.

Please refer to sub-protocols for additional information regarding additional investigational agents pertinent to specific sub-protocols.

1.2. Background on DAY101

1.2.1. DAY101 Nonclinical Data

A comprehensive package of nonclinical studies has been conducted with DAY101 and provides a thorough pharmacological and toxicological profile of DAY101 in multiple species, as detailed in the Investigator's Brochure (IB).

DAY101 has been extensively studied in both *in vitro* and *in vivo* systems and has been found to result in potent inhibition of downstream signaling of the BRAF V600E mutation (Olszanski et al. 2017). In contrast to the approved Type-I BRAF inhibitors (e.g., vemurafenib, dabrafenib, and encorafenib), DAY101 inhibits both wild-type BRAF and CRAF/RAF1 kinases, BRAF V600E mutation and, importantly, hyperactivated signaling resulting from BRAF fusions, including the KIAA1549:BRAF fusion (Sun et al. 2017). *In vitro* studies have demonstrated that DAY101 [redacted] signaling, along with cell proliferation, in a wide array of cell lines harboring RAF or RAS alterations. *In vivo* pharmacokinetic (PK)-pharmacodynamic (PD) studies have shown that [redacted] harboring BRAF mutations, RAS mutations, or KIAA1549:BRAF fusions. [redacted] was observed in xenograft tumor models in response to monotherapy treatment with DAY101.

DAY101 has been shown to inhibit the kinase activity of BRAF in the context of BRAF kinase domain fusions with various 5′ gene partners, most notably fusion with the KIAA1549 gene. KIAA1549:BRAF fusion kinase activity is inhibited by DAY101 with comparable potency to inhibition of BRAF V600E in cell model systems. (Sun et al. 2017).

Importantly, in contrast to Type-I BRAF inhibitors, DAY101 does not result in paradoxical activation of MAPK signaling in BRAF fusion expressing cells (Sun et al. 2017), which limits the use of Type-I BRAF inhibitors. In contrast to MEK inhibitors, DAY101 directly inhibits BRAF dimers, [redacted] As detailed below, the profile of DAY101 does not appear to have [redacted] liabilities of the incumbent RAF or MEK inhibitors. Finally, compared to approved BRAF inhibitors, DAY101 has [redacted] in preclinical rodent models (Sun et al. 2017, Gampa et al 2019).

DAY101 has been characterized extensively for pharmacokinetic (PK; intravenous and oral routes) and toxicokinetic (TK) profiles in rats and cynomolgus monkeys using the oral route of administration, which is the intended clinical route. Refer to the DAY101 IB for details on these nonclinical studies.

DAY101 showed [redacted] in all species tested with a free fraction of [redacted] in [redacted] Following a single oral administration of [^{14}C] DAY101 to pigmented Long Evans (LE) rats, [redacted] was widely distributed to [redacted] DAY101 demonstrated [redacted] penetration in this study, wherein DAY101 derived [redacted] had the [redacted] exposure (AUC_{0-24}) ratio of [redacted] in rats.

Two metabolic enzyme phenotyping studies suggest that DAY101 is primarily metabolized by aldehyde oxidase (AO), followed by [redacted] The relative contribution was [redacted]%, [redacted]%, [redacted]%, [redacted]% and [redacted]% for AO, [redacted] respectively. Therefore, the risk for DAY101 exposure to be affected by coadministration with [redacted] inhibitors is considered low.

In vitro, DAY101 showed [redacted] of major [redacted] enzymes and was not a time-dependent inhibitor of any major [redacted]. *In vitro* DAY101 did not [redacted] and the [redacted] however, more than [redacted] increase in [redacted] levels in three different donor lots of [redacted] was observed for [redacted] Further investigation using Simcyp physiological based pharmacokinetic modeling and simulation (PBPK) simulator predicted DAY101 to be a moderate [redacted] inducer [redacted] at the [redacted] mg once weekly (QW) dose. Based on *in vitro* interactions with [redacted] DAY101 is [redacted] a substrate for [redacted] is not a clinically meaningful inhibitor for [redacted] but it is a [redacted] inhibitor with IC_{50} value of [redacted] µM. Based on Simcyp PBPK modeling, DAY101 is predicted to increase the AUC of rosuvastatin (a [redacted] substrate) by [redacted]%.

1.2.2. DAY101 Clinical Data

Two clinical studies (Studies C28001 and C28002; [redacted] in adult patients with advanced solid tumors were completed by the previous Sponsor. In addition, 1 investigator-initiated clinical study (Study [redacted] Study: [redacted]) and a registrational Phase 2 study (Firefly-1/Study PNOC026 [redacted] are ongoing with DAY101 in pediatric patients with relapsed and refractory pediatric low-grade glioma

(pLGG). Study conduct for a relative [redacted] study in healthy subjects (Study [redacted] has also been completed.

Study C28001 was a Phase 1 First -In -Human (FIH) study conducted in adult patients with advanced solid tumors. DAY101 was administered orally (PO) once every other day (Q2D) in 22- and 28-day treatment cycles, at doses of 20, 40, 80, 135, 200, and 280 mg. DAY101 was also administered QW in 28-day treatment cycles with a starting dose of 400 mg, then 600 and 800 mg. The adult maximum tolerated doses (MTDs) were reached at 200 mg Q2D and 600 mg QW. Expansion cohorts included patients with advanced, metastatic, or unresectable melanoma with MAPK alterations. Details of this study can be found in the DAY101 IB.

Study C28002 was a Phase 1b study conducted in patients with advanced, solid tumors for whom standard therapies had failed. This study was conducted as an "umbrella study" in which DAY101 was studied in combination with various chemotherapy agents or targeted therapies in adult patients with either advanced CRC or advanced NSCLC (with either KRAS exon 2 mutations or non-V600 BRAF mutations). Details of this study can be found in the DAY101 IB.

Study [redacted]

[redacted]

Study [redacted]

[redacted]

Study FIREFLY-1/PNOC026

Sponsor is currently conducting a pivotal Phase 2, open-label study to evaluate the safety and efficacy of DAY101 monotherapy in the treatment of RAF-altered, recurrent, or progressive low-grade gliomas or advanced solid tumors. This study is expected to enroll approximately 140 pediatric and young adult patients 6 months to 25 years of age. This study includes 3 arms. Arm 1 (N = 60) serves as the main cohort to evaluate DAY101 in the treatment of patients with recurrent or progressive low-grade glioma harboring a known activating BRAF alteration. Study results of Arm 1 will be the basis of DAY101's initial regulatory license application. Arm 2 (N = 60) is enrolling a similar patient population to Arm 1 based on the recommendation of a Data Safety Monitoring Board (DSMB) and is aimed to provide continuous access to DAY101 prior to commercial availability. In addition, Arm 3 is enrolling patients with advanced solid tumors harboring RAF fusions (e.g., BRAF or CRAF/RAF1 fusions).

As of 11 April 2022, Arm 1 has fully accrued and was closed to enrollment. The study is ongoing.

1.2.2.1. Clinical Pharmacokinetics

Details of the PK from Studies C28001, [redacted], and [redacted] are included in Section 1.3.2, as well as in the IB.

1.2.2.2. Clinical Efficacy

Study C28001

Antitumor activity was most evident in the BRAF mutation -positive treatment -naïve expansion melanoma cohort using 200 mg Q2D regimen (ORR: 8/16 patients, 50% [95% confidence interval (CI) 25, 75]; median duration of response (DOR) [partial response (PR) in 8 patients]: 6.0 months [95% CI: 3.7, not estimable]; median progression-free survival (PFS): 5.7 months [95% CI: 1.9, 14.3]). A PR was also reported in 1 of 6 patients in the BRAF mutation -positive previously treated cohort (ORR: 17%; 95% CI: < 1, 64). Another PR was reported in 1 of 14 patients in the NRAS mutation-positive MAK kinase treatment naïve cohort (ORR: 7%; 95% CI: < 1, 34).

Further details of the efficacy data from C28001 can be found in the DAY101 IB.

Study [redacted]

Study FIREFLY-1/PNOC026

As of 14 April 2022, 25 patients had at least 2 post-baseline radiographic assessments (performed every 3 cycles). Out of 25 patients dosed, 3 patients were determined by the independent review committee (IRC) to lack measurable lesion(s) meeting the RANO-high-grade glioma (HGG) criteria definition for measurability at baseline (Wen et al. 2010) and were thus excluded from the efficacy analysis (n = 22).

Response data presented in the tables below are based on evaluation by IRC using RANO-HGG criteria. Table 1 includes best overall confirmed response by BRAF alteration. Of these 22 patients, 13 (59.1%) have achieved a confirmed partial response. Additionally, one patient with a best overall response (BOR) of stable disease achieved an unconfirmed partial response (reduction of 50% from baseline) at the most recent radiographic assessment and remains on treatment. In addition, duration of response ranged from approximately 3 to 8 months. As of the data cutoff of 14 April 2022, all responses were ongoing.

Of the 22 patients included in the analysis, 5 patients have discontinued, 3 due to progressive disease and 2 due to withdrawal of consent. No patients with a documented response (confirmed or unconfirmed) have discontinued due to toxicity or disease progression.

Table 1: Confirmed Best Overall Response and Overall Response Rate (Study FIREFLY-1/PNOC026)

Best Overall Response, N (%)	BRAF Mutation n = 2	BRAF Fusion[a] n = 20	Total Efficacy Evaluable N = 22
CR	0	0	0
PR	2 (100.0)	11 (55.0)	13 (59.1)
unconfirmed PR[b]	0	1 (4.5)	1 (4.5)
SD	0	6 (30.0)	6 (27.3)
PD	0	2 (10.0)	2 (9.1)
Overall Response Rate (95% CI)[c]	100% (15.8–100)	60.0% (36.1–80.9)	63.6% (40.7–82.8)

Abbreviations: CI, confidence interval; CR, complete response; FISH, fluorescence in situ hybridization; PD, progressive disease; PR, partial response; SD, stable disease.
a. BRAF Fusion includes KIAA1549:BRAF fusion as identified by next-generation sequencing or dual-probe FISH and BRAF rearrangements as identified by break-apart FISH.
b. One patient had an unconfirmed PR at the time of data cutoff, where the confirmation scan was not read by IRC.
c. Includes patients with best overall response of CR, PR, and unconfirmed PR.
Source: DAY101 Investigator's Brochure

1.2.2.3. Clinical Safety

Study C28001

Over the life of this study, which was completed on 16 October 2018, 110 patients were administered at least 1 dose of DAY101 on a Q2D dose schedule (30 in the dose-escalation phase and 80 in the dose-expansion phase). Thirty-nine patients were administered at least 1 dose of DAY101 on a QW dose schedule (20 in the QW dose escalation phase [3 in the 400 mg cohort, 13 in the 600 mg cohort, and 4 in the 800 mg cohort] and 19 dosed at 600 mg QW in the expansion phase). The monotherapy treatment of 149 adults has provided a comprehensive database of safety information.

Of the 149 patients treated, all had at least 1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs across all dose cohorts in the Q2D dose-escalation phase included fatigue (67%), maculopapular rash (37%), and arthralgia and constipation (30% each). The most frequently reported TEAEs in the Q2D dose-expansion phase included fatigue (43%), anemia (41%), constipation and maculopapular rash (38% each), nausea (36%), and dyspnea (30%).

The most frequently reported TEAEs across all dose cohorts in the QW dose-escalation phase included fatigue (55%), anemia (40%), nausea (35%), and headache (30%). In the QW dose-expansion cohort, the most frequently reported TEAE was fatigue (47%). More details can be found in the DAY101 Investigator's Brochure.

Table 2: TEAEs Reported for ≥ 10% of Adult Patients with Advanced Solid Tumors Overall (Safety Population) (Study C28001)

Preferred Term	Dose-Expansion Phase		
	Q2D Total N = 80 n (%)	QW Total N = 19 n (%)	Total N = 99 n (%)
Patients with at least 1 Treatment-Emergent AE	80 (100)	19 (100)	99 (100)
Fatigue	34 (43)	9 (47)	43 (43)
Anaemia	33 (41)	4 (21)	37 (37)
Constipation	30 (38)	4 (21)	34 (34)
Nausea	29 (36)	5 (26)	34 (34)
Rash maculo-papular	30 (38)	3 (16)	33 (33)
Dyspnoea	24 (30)	4 (21)	28 (28)
Blood creatine phosphokinase increased	23 (29)	1 (5)	24 (24)
Myalgia	20 (25)	3 (16)	23 (23)
Vomiting	16 (20)	3 (16)	19 (19)
Decreased appetite	14 (18)	4 (21)	18 (18)
Pruritus	16 (20)	1 (5)	17 (17)
Pyrexia	14 (18)	3 (16)	17 (17)
Dysgeusia	16 (20)	1 (5)	17 (17)
Periorbital oedema	14 (18)	2 (11)	16 (16)
Aspartate aminotransferase increased	16 (20)	0	16 (16)
Arthralgia	11 (14)	4 (21)	15 (15)
Oedema peripheral	15 (19)	0	15 (15)
Diarrhoea	13 (16)	1 (5)	14 (14)
Dermatitis acneiform	12 (15)	2 (11)	14 (14)
Pain in extremity	14 (18)	0	14 (14)
Hair colour changes	13 (16)	1 (5)	14 (14)
Headache	11 (14)	2 (11)	13 (13)
Back pain	12 (15)	1 (5)	13 (13)
Cough	10 (13)	2 (11)	12 (12)
Abdominal pain	9 (11)	1 (5)	10 (10)

Study C28002

Study C28002 [redacted] was an open-label study designed to evaluate DAY101 in combination with MLN0128, alisertib, paclitaxel, cetuximab, or irinotecan. During both dose escalation and dose expansion where 81 patients were enrolled (71 patients in the dose-escalation phase and 10 patients in the dose-expansion phase), the most commonly reported TEAE was hypophosphatemia (41 patients [58%] and 7 patients [70%], respectively). Grade 3 or higher TEAEs were reported for 59 patients (83%) during dose

escalation and 9 patients (90%) during dose expansion. Overall, the most commonly reported Grade ≥ 3 TEAEs were hypophosphatemia, reported for 27 patients (38%) during dose escalation and 6 patients (60%) during dose expansion, and anemia, reported for 19 patients (27%) during dose escalation and 4 patients (40%) during dose expansion. More details can be found in the DAY101 IB.

Study [redacted]

[redacted]

Table 3: Grade ≥ 3 Adverse Events Occurring in ≥2 Patients by Preferred Term (Study [redacted]

Sponsor Modified Term	CTCAE Grade	Total (N = [redacted]) N (%)
Vomiting	[redacted]	
Hypophosphatemia		
Rash maculopapular		
CPK increased		
Hydrocephalus		
Fatigue		
Nausea		
Device related infection		
Headache		

Abbreviations: CPK, creatine phosphokinase; CTCAE, Common Terminology Criteria for Adverse Events; N, number.
Source: DAY101 Investigator's Brochure

The [redacted] study has completed patient accrual, and follow-up for enrolled patients is ongoing as of the date of this protocol.

Study FIREFLY-1/PNOC026

Safety data from the first 25 patients enrolled on FIREFLY-1/PNOC026 are summarized in Table 4 below. DAY101 is well-tolerated, and most treatment-emergent AEs were deemed Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. The most common CTCAE Grade ≥ 3 treatment-emergent AEs, , were rash (3 patients [12%]) anemia, blood CPK increase (2 patients each [8%]). and vomiting (1 patient [4%]). Seven patients (28%) required dose modification due to treatment-related AEs; however, no patient discontinued treatment due to AE at the time of data cutoff.

Table 4: Incidence and Percentage of Treatment-Emergent and Treatment-Related AEs (Study FIREFLY-1/PNOC026)

Preferred term, N (%)	Treatment-emergent AEs		Treatment-related AEs	
	Any Grade	CTCAE Grade ≥ 3	Any Grade	CTCAE Grade ≥ 3
Blood creatine phosphokinase increased	20 (80)	2 (8)	18 (72)	2 (8)
Hair color changes	17 (68)	-	17 (68)	-
Anemia	14 (56)	3 (12)	10 (40)	2 (8)
Aspartate aminotransferase increased	14 (56)	-	12 (48)	-
Vomiting	14 (56)	2 (8)	6 (24)	1 (4)
Rash[a]	13 (52)	3 (12)	13 (52)	3 (12)
Blood lactate dehydrogenase increased	12 (48)	-	9 (36)	-
Headache	10 (40)	-	3 (12)	-
Dry skin	9 (36)	-	7 (28)	-
Epistaxis	9 (36)	-	4 (16)	-
Constipation	8 (32)	-	5 (20)	-
Hypocalcemia	8 (32)	-	6 (24)	-
Nausea	8 (32)	-	3 (12)	-
Alanine aminotransferase increased	7 (28)	1 (4)	4 (16)	1 (4)
Fatigue	7 (28)	-	7 (28)	-

Abbreviations: AE, adverse event; INR, international normalized ratio.
a. Includes maculopapular and erythematous rash
Source: DAY101 Investigator's Brochure

1.3. Study Rationale and Dose Justification

1.3.1. Study Rationale

In the MAPK signaling pathway, kinase inhibitor-mediated inhibition of oncogenic driver alterations (such as mutations in BRAF, KRAS, NRAS, or RAF fusions) can lead to an antitumor response due to "addiction" of the cancer to the activated pathway. However, acquired resistance can occur due to multiple adaptive mechanisms including relief of negative feedback that can drive ERK reactivation (Johnson et al. 2014; Johnson and Puzanov 2015). Interestingly, inhibition of 2 nodes of the MAPK pathway such as combination of BRAF and MEK inhibition has been shown to provide more lasting clinical benefit compared to inhibition of only BRAF alone (Long et al. 2017). Therefore, we propose in this "umbrella design" Master Protocol to evaluate DAY101, a Type-II RAF inhibitor that can bind both monomeric and dimeric forms of RAF, as a therapeutic monotherapy and in combination in order to drive deeper and more durable responses in biomarker-defined cancers. Sub-protocols under this Master Protocol will explore the use of

DAY101 as monotherapy in oncogenic addicted tumors, such those harboring as BRAF/CRAF fusions or CRAF/RAF1 amplifications, as well as the use of DAY101 in combination with other therapies, particularly those that target the MAPK pathway (e.g., MEK or ERK inhibitors), in order to achieve vertical MAPK pathway inhibition, which has been shown in preclinical studies to inhibit the growth of tumors harboring specific MAPK pathway aberrations.

1.3.2. Justification for Dose

A sustained, high degree of target inhibition in tumor tissue appears to be necessary for maximal activity for RAF and MEK inhibitors in adult solid tumors, both in nonclinical models and in clinical trials (Flaherty et. al. 2010). In preclinical pharmacodynamic studies in tumor-bearing mice, DAY101 caused [redacted] of MAPK pathway activation at a dose of [redacted] mg/kg (> [redacted] % [redacted] for up to [redacted] hours following [redacted] This dose also [redacted] models, on [redacted] dosing schedules. This [redacted] of RAF is expected to translate to the clinical setting because the mean half-life ($t_{1/2}$) of DAY101 is [redacted] in humans [redacted] hours) than in mice [redacted] hours). Therefore, administering DAY101 on a once weekly schedule was expected to provide the required degree of target inhibition over the [redacted] hour dosing interval.

Favorable efficacy and safety profiles were observed in initial data from Study FIREFLY-1 in pLGG patients.

The low rate of accumulation of DAY101 with the once weekly dose schedule enables continuous exposure at a steady-state concentration that inhibits BRAF driven disease while reducing the risk of toxicity due to drug accumulation, as confirmed by exposure-AE modeling.

Study C28001

The PK of DAY101 has been well-characterized in the dose-escalation phases of the FIH, Phase 1 Study C28001 in adult patients with advanced solid tumors. In Study C28001, DAY101 was administered PO Q2D in 22-day and 28-day treatment cycles at doses of 20, 40, 80, 135, 200, and 280 mg. DAY101 was also administered QW in 28-day treatment cycles with a starting dose of 400 mg, then 600 and 800 mg. The adult MTDs were reached at 200 mg Q2D and 600 mg QW.

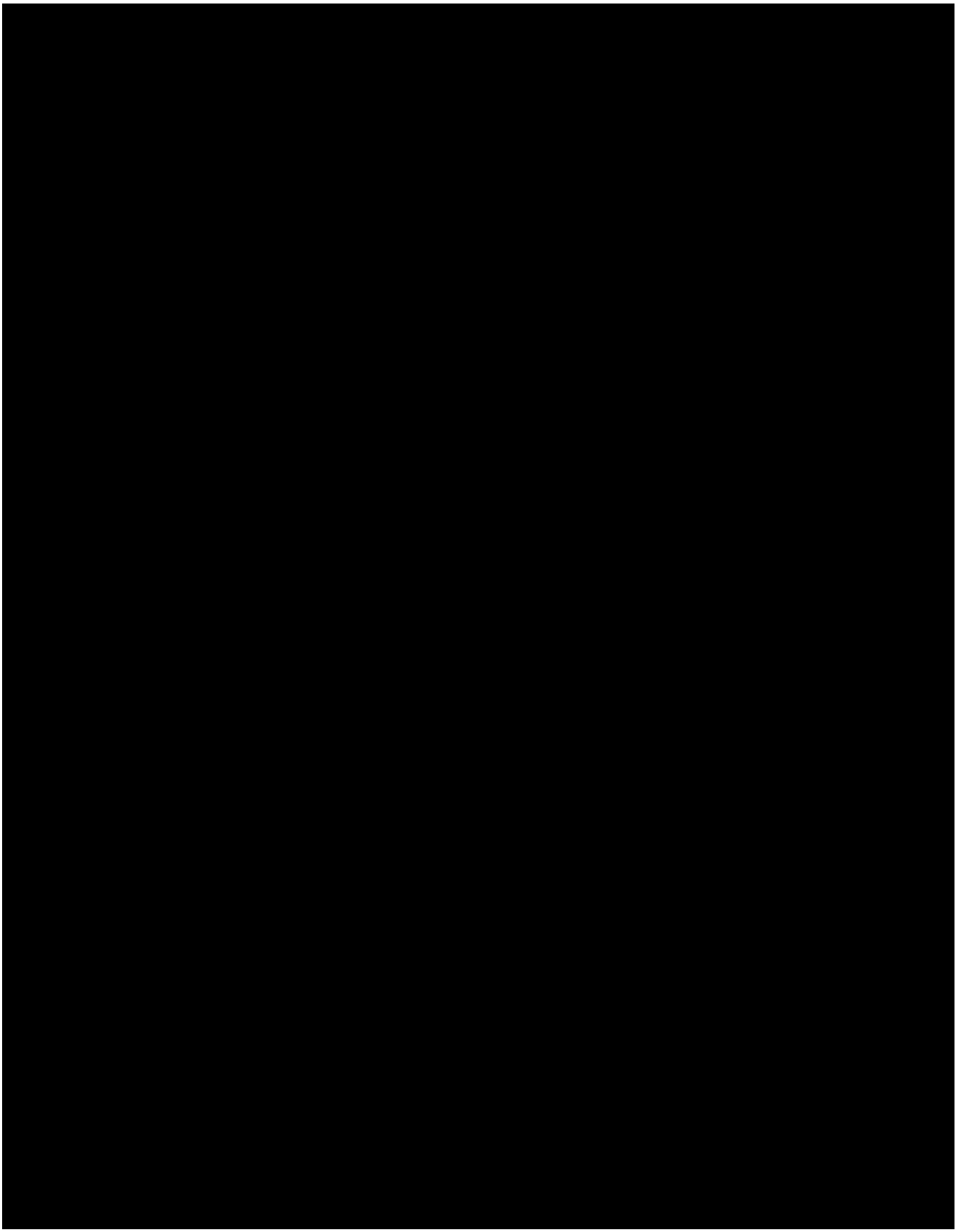
DAY101 was absorbed into systemic circulation following oral administration with a median time to maximum concentration between 2 and 4 hours post-dose. Steady-state DAY101 area under the concentration-time curve (AUC) increased in an approximately dose-proportional manner over the dose ranges of 20 to 280 mg Q2D and 400 to 800 mg QW. Administration of DAY101 PO Q2D resulted in approximately 2.5-fold accumulation in area under the concentration-time curve from time zero to 48 hours at steady state. No apparent accumulation was observed with the once-weekly dose regimens. The mean terminal half-life ($t_{1/2}$) of DAY101 was 70 hours. At both 200 mg Q2D and 600 mg QW, DAY101 AUC exceeded the AUC (111,000 ng • h/mL) associated with 83% tumor growth inhibition in the WM-266-4 melanoma xenograft model.

Study [redacted]

[redacted]

Study [redacted]

[redacted]



[redacted]

1.3.3. Drug Metabolism for DAY101

DAY101 is metabolized primarily by AO, while the remaining contribution to DAY101 metabolism comes from multiple [redacted] most notably [redacted] Therefore, concurrent strong [redacted] inhibitors or inducers are prohibited while taking DAY101.

The sub-protocols under this Master Protocol will explore the use of DAY101 as monotherapy as well as the use of DAY101 in combination with other therapies, to achieve inhibition of the MAPK and potentially other pathways. Alternative dose and schedule may be further explored based on synergies observed in preclinical studies (Ozkan-Dagliyan et al. 2020; Fernandes et al. 2020). Specific dose justification will be provided within each sub-protocol.

1.3.4. Benefit/Risk

When viewed as a whole, the preclinical data and early clinical data indicate that DAY101 as monotherapy is a highly potent and specific inhibitor of the RAF alterations, with minimal off-target inhibition of other kinases. Preclinical data evaluating the antitumor activity of DAY101 in combination with MEK inhibitors indicates the potential for clinical benefit in solid tumors with genomic alterations not currently addressed by available therapies.

The clinical efficacy of DAY101 has been evaluated in the completed Phase 1 FIH single-agent study (Study C28001) and the completed Phase 1b combination-therapy study (Study C28002) in adult patients with advanced solid tumors. In Study C28001, during dose expansion, ORR was 50% in melanoma patients with BRAF V600E mutations treated with DAY101 200 mg Q2D. In Study C28002, during dose expansion in NSCLC patients with KRAS mutation, partial response was 38% in a cohort treated with DAY101 in combination with paclitaxel. DAY101 has been administered to [redacted] Centrally reviewed radiographic assessments are available from 9 patients enrolled into the dose-escalation portion of the study (Wright 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 CR or PR with a median TTR of 10.5 weeks. In addition, 77 pediatric low-grade glioma patients have been dosed with DAY101 in Arm 1 of the FIREFLY-1/PNOC026 study [redacted] As of 14 April 2022, 25 patients had at least 2 post-baseline radiographic assessments (performed [redacted] Out of 25 patients dosed, 3 patients were determined by the IRC to lack measurable lesion(s) meeting the RANO- HGG criteria definition for measurability at baseline (Wen et al. 2010) and were thus excluded from the efficacy analysis (n = 22). Of these 22 patients, 13 (59.1%) have achieved a confirmed partial response. Additionally, one patient with a BOR of stable disease achieved an unconfirmed partial response (reduction of 50% from baseline) at the most recent radiographic assessment and remains on treatment. In addition, duration of response ranged from approximately 3 to 8 months. As of the data cutoff of 14 April 2022, all responses were ongoing.

Because DAY101 is an experimental medicine, it is possible that unforeseen, unknown, or unanticipated drug reactions and toxicities may occur. Based on prior clinical studies in adults, frequently reported adverse events observed with DAY101 monotherapy at the QW dosing regimen were fatigue (50% all grade, 5% Grade 3), rash (13%, primarily Grade 1 and 2), anemia (30% of patients, all Grade; 10% of patients, Grade ≥ 3), and gastrointestinal events (all Grades 1 and 2). Other notable laboratory abnormalities were aspartate aminotransferase (AST) elevation, and increased creatine phosphokinase levels. In pediatric studies to date, the safety profile of DAY101 at the QW dosing regimen has been consistent with adult clinical trial data. However, as detailed below, this clinical protocol is designed to mitigate risks to patients primarily through eligibility criteria, dose modifications for toxicities, guidelines for toxicity recognition and management of common events. A detailed plan for careful safety monitoring, systematic review of adverse events, monitoring and reporting of serious adverse events (SAEs) and adverse events of special interest (AESIs), evaluation of PK, and active pharmacovigilance review to assess for safety signals or trends has been implemented.

Patients, both adults and adolescents, with aberrations in the key proteins of the MAPK pathway who have exhausted standard-of-care treatment represent populations with high unmet need as discussed in Section 1.1. Therefore, there is an urgent need to identify new Type II pan-RAF inhibitors that can inhibit these both RAF monomers and dimers and limit AEs associated with these agents.

Taken together, these considerations indicate the benefit/risk ratio for treatment with DAY101 to be favorable.

Additional therapies in combination with DAY101 may be investigated based on the scientific and therapeutic hypotheses outlined above. For further details related to benefit/risk with the combination, please see relevant sub-protocols.

2. STUDY OBJECTIVES

Specific objectives and corresponding endpoints for the master study and sub-studies are outlined in Table 5 and Table 6 below. Additional objectives and endpoints may be specified according to the relevant sub-protocol.

The Phase 1b objectives will only apply to sub-studies of DAY101 in combination with other therapies (Table 5).

The Phase 2 objectives will apply to the investigation of DAY101 as monotherapy and in combination with other therapies. Additional objectives will be specified according to the relevant sub-protocol (Table 6).

Table 5: Phase 1b Study Objectives and Endpoints

PRIMARY OBJECTIVE AND ENDPOINTS IN PHASE 1B	
OBJECTIVE	**ENDPOINTS**
To determine the safety of DAY101 in combination with other therapies.	• Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Advanced Tumours (NCI CTCAE) v5 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
To determine the maximum tolerable does (MTD) and recommended Phase 2 dose (RP2D) of DAY101 in combination with other therapies.	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Incidence of dose-limiting toxicities (DLTs)
SECONDARY OBJECTIVES AND ENDPOINTS IN PHASE 1B	
OBJECTIVE	**ENDPOINTS**
To assess the efficacy of DAY101 in combination with other therapies by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or appropriate tumor response criteria.	• ORR as assessed by the proportion of patients with the best overall confirmed response of complete response (CR) or partial response (PR) according to the appropriate tumor response criteria as assessed by Investigator • Duration of response (DOR) in patients with best overall response of CR or PR as determined by the treating Investigator [from time of first tumor response to progression or date of data analysis, whichever occurs earlier] • Duration of progression-free survival (PFS) following initiation of study treatment to disease progression,

	death, or date of analysis, whichever occurs earlier according to the appropriate tumor response criteria • Duration of overall survival (OS) following initiation of study treatment to time of death • Time to response (TTR) in patients with best overall response of CR or PR as determined by treating Investigator [from initiation of study treatment to date of first response] • Comparing the DOR in patients with CR or PR as determine by treating Investigator with the DOR observed with the immediate prior line of anticancer treatment
To characterize the pharmacokinetic (PK) profile of DAY101 in combination with other therapies.	• Plasma concentration of DAY101 at specified time points in order to define PK parameters
To characterize pharmacodynamic (PD) effects of DAY101 in combination with other therapies.	• PD to be assessed by relevant assay or platform including but not limited to RNA sequencing and immunohistochemistry (Please see Appendix E).
EXPLORATORY OBJECTIVES AND ENDPOINTS IN PHASE 1B	
OBJECTIVES	**ENDPOINTS**
To evaluate the genomic profile of archival tumor biopsies or fresh tumor biopsies (if available) from patients who will be treated with DAY101 in combination with other therapies.	• Assess genomic alterations from archival tumor biopsy or fresh tumor specimens using a relevant platform(s) such as, but not limited to, next-generation sequencing and circulating tumor DNA (ctDNA)
To characterize pathway modulation, and/or genomic alterations in tumor biopsies.	[redacted]
To characterize genomic alterations in ctDNA.	

[redacted]

Table 6: Phase 2 Study Objectives and Endpoints

PRIMARY OBJECTIVE AND ENDPOINTS IN PHASE 2	
OBJECTIVE	**ENDPOINTS**
To evaluate the efficacy of DAY101 by RECIST version 1.1 or appropriate tumor response criteria as a monotherapy, or in combination with other therapies.	• Overall response rate (ORR) as assessed by the proportion of patients with the best overall confirmed response of complete response (CR) or partial response (PR) according to the appropriate response assessment criteria for the disease setting as assessed by the Investigator
SECONDARY OBJECTIVES AND ENDPOINTS IN PHASE 2	
OBJECTIVE	**ENDPOINTS**
To assess the safety and tolerability of DAY101 as monotherapy, or in combination with other therapies.	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test result
To assess additional efficacy parameters of DAY101 as monotherapy or in combination with other therapies.	• DOR in patients with best overall response of CR or PR as determined by the treating Investigator [from time of first tumor response to progression or death, whichever occurs earlier] • Duration of progression-free survival (PFS) following initiation of study treatment to disease progression or death, whichever occurs earlier according to the appropriate tumor response criteria • Duration of OS following initiation of study treatment to time of death
To characterize the tumor responses observed with DAY101 as monotherapy or in combination with other targeted therapies.	• Time to response (TTR) in patients with best overall response of CR or PR as determined by treating Investigator [from initiation of study treatment to date of first response]
To characterize the pharmacokinetic (PK) profile of DAY101 in combination with other therapies.	• Plasma concentration of DAY101 at specified time points in order to define PK parameters
To characterize pharmacodynamic (PD) effects of DAY101 in combination with other therapies.	• PD to be assessed by relevant assay or platform including but not limited to RNA sequencing and immunohistochemistry (Please see Appendix E).
To determine the relationship between PK and PD of DAY101 in combination with other therapies.	• Determine the relationship between PK and PD biomarkers

EXPLORATORY OBJECTIVES AND ENDPOINTS IN PHASE 2	
OBJECTIVES	**ENDPOINTS**
[redacted]	
To evaluate the genomic profile of archival tumor or fresh tumor biopsies from patients who will be treated with DAY101 as monotherapy or in combination with other therapies.	• Assess genomic alterations from archival or fresh tumor biopsy specimens using a relevant platform such as but not limited to ctDNA and next-generation sequencing
To characterize pathway modulation and/or genomic alterations from tumor biopsies.	[redacted]
To characterize genomic alterations from ctDNA.	
[redacted]	

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a Phase 1b/2, multi-center, open-label, umbrella study of patients ≥ 12 years of age with recurrent or progressive solid tumors with alterations in the key proteins of the RAS/RAF/MEK/ERK pathway, which will be referred to as the MAPK pathway. 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.

Based on the identified alterations in the key proteins of the MAPK pathway, patients may be offered the opportunity to participate in one or more sub-protocols within this umbrella study of DAY101 as monotherapy or in combination with other therapies. Enrollment will be based on the specific eligibility criteria described in each sub-protocol.

Study DAY101-102 (master study) and sub-protocols 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 as specified in the sub-protocol. Additional dose schedules may be explored. Dose level(s), dose schedule(s), and cycle lengths for DAY101 as monotherapy or in combination with other therapies will be specified in each sub-protocol.

Cycles will repeat, as specified in each sub-protocol, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

Patients will undergo radiographic evaluation of their disease at baseline, at the end of [redacted] for 1 year and then [redacted] thereafter, or as specified in a given sub-protocol. 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 RANO criteria. Appropriate response criteria for tumors are described in Appendix B and Appendix C.

Patients who have radiographic evidence of disease progression may be allowed to continue DAY101 (and combination partner if applicable) 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.

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

Other therapies may be included in future sub-protocols and will be further specified within each sub-protocol.

Scheduled activities will be performed in as outlined in the Schedule of Activities within each sub-protocol. The study design schema is shown in Figure 3. Refer to the relevant sub-protocol for each sub-protocol design schema.

Figure 3: Study Design Schema

3.1.1. End of Study and Length of Study

For details related to end of study and length of study, please see relevant sub-protocols.

3.1.2. Number of Patients

Maximum number of patients enrolled will be dependent on the sub-studies included. Please refer to specific sub-protocol for more detail.

3.2. Investigational Sites

Refer to the sub-protocols for the number of institutions participating 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. Inclusion and exclusion criteria can be found within each sub-protocol.

5. TREATMENT

5.1. Investigational Product

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

The site pharmacist will dispense the tablets to the patient, or to the patient's parent or legal guardian, in an amount necessary to allow for outpatient administration. Further information is provided in the Pharmacy Manual.

DAY101 tablets are to be stored at controlled room temperature (between 15°C and 30°C) and protected from light. Additional details regarding the investigational product are provided in the DAY101 IB.

Additional therapies may be included. For further details, please see relevant sub-protocols.

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 must 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 or 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 or 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 nurse. The study drug administration diary will also be assessed at each clinic visit.

For additional dosing administration instruction for each sub-protocol, please refer to individual sub-protocol for details.

5.2.2. Dose-Limiting Toxicity

Assessment of DLT will be further specified in relevant sub-protocols.

5.2.3. Dose Modifications

Please refer to the sub-protocols for study drug modifications and reduction details.

5.2.4. Management of Treatment-Related Events

Please refer to the sub-protocols for study drug modifications and treatment-related events management guidelines for DAY101 and/or combination partners.

5.3. Removal of Patients from Therapy or Assessment

Patients may withdraw from the study at any time. Patients who withdraw from therapy and do not withdraw consent will be referred to as "discontinue study treatment" and will be followed for LTFU. Over the course of the study, a patient may discontinue from study treatment for any of the reasons listed below:

- Disease progression as assessed by the Investigator, except if, in the opinion of the Investigator and with permission of the Sponsor, the patient is deriving clinical benefit from continued study treatment
- Unacceptable toxicity
- Intercurrent illness compromising the ability to fulfill protocol requirements
- Dosing interruption > 28 days, unless resumption of treatment approved by the Sponsor
- Requirement for alternative treatment in the opinion of the Investigator
- Significant noncompliance to protocol
- Pregnancy
- Withdrawal of consent or assent by the patient or the patient's parent or legal guardian
- Loss to follow-up
- Death

When a patient discontinues from treatment, the patient will undergo the end of treatment (EOT) visit, as outlined in Section 6.24 .

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 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. Please refer to the sub-protocols for eligibility criteria and specific concomitant mediation information.

5.4.2. Allowed Concomitant Medications

Please refer to the sub-protocols for specific allowed concomitant medications.

5.4.3. Prohibited Concomitant Medications

Please refer to the sub-protocols for specific prohibited concomitant medications.

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.

Please see each sub-protocol for instruction on holding DAY101 and other investigational drugs.

5.4.5. Concurrent Surgery

Patients may undergo surgical intervention and remain on study when, in the opinion of the treating Investigator, surgery is indicated for anything other than tumor resection for clinical or radiographic disease progression. Therapy should be held for 6 days before surgical intervention. Patients undergoing surgical intervention are permitted to restart study treatment 6 days following surgical intervention after discussion with and approval by the Sponsor. The surgical intervention should be recorded on the appropriate electronic case report form (eCRF). For patients requiring surgical intervention due to clinical or radiographic evidence of tumor progression, patients should be withdrawn from study.

5.5. Preparation, Handling, Storage and Accountability

1. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug(s) received and that any discrepancies are reported and resolved before use.
2. Only participants enrolled in the study may receive study drug(s) and only trained site staff may supply or administer study treatments.
3. The Investigator, institution, or head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study drug(s) tablets are provided in the Pharmacy Manual.

6. TESTS AND EVALUATIONS

All required observations and schedules are described in more detail in Sections 6.1 through 6.27.

Most study assessments and procedures (including treatment administration) will be performed in cycles, defined as 28-day intervals starting with the date of DAY101 administration at baseline unless otherwise specified in the sub-protocol. In the absence of toxicity, all scheduled visits will occur within windows for the protocol-specified visit schedule. If the patient is unable to have a study assessment within the defined time window due to an event outside of his or her control (e.g., clinic closure or travel restrictions due to COVID-19, personal/family emergency, inclement weather), the assessment should be performed as close as possible to the required schedule.

6.1. Screening

The screening procedures must be conducted within 28 days prior to [redacted] unless otherwise noted. Patients who cannot complete the procedures within the screening window may be rescreened as many times as the Investigator deems appropriate. Procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study do not need to be repeated, with the exception of tumor imaging, which must be repeated if the prior imaging does not collect the appropriate sequences required for study as defined in the Imaging Manual.

Screening tests that are completed in the 48 hours prior to start of DAY101 and duplicate [redacted] tests according to the Schedule of Activities (see subprotocol(s) for specific schedule(s) of assessments) will be accepted as fulfilling the [redacted] assessments. Repeat testing on [redacted] is not necessary for this scenario, and results should be recorded in the screening set of eCRFs.

A completed screening form and supportive materials will be sent to the Sponsor or designee when a potential study candidate is identified. Any reports (e.g., pathology report, MRI report) supportive to the screening form must have Protected Health Information (name, date of birth, address, parents' names, medical record number, etc.) removed prior to submission to Sponsor. The site representative will be contacted by either the Sponsor or its designee to 1) confirm eligibility or 2) provide additional information.

Patients who are determined to be screen failures can be rescreened. Rescreened patients will maintain the same unique patient number assigned to them originally by the Sponsor. A revised screening form should be submitted to the Sponsor or its designee for rescreened patients. See the Study Binder for enrollment form, patient number assignment, contact numbers, and other details of enrollment.

The approved screening form will be returned to the site with the cohort assignment (if applicable) as verification of eligibility in the trial, and for record-keeping purposes.

6.2. Enrollment

Enrollment procedures will be conducted in accordance with the Schedule of Activities (see subprotocol(s) for specific schedule(s) of assessments). Patients who meet the eligibility

criteria, as outlined in each sub-protocol, will be enrolled in this study. Procedure details, timing and details regarding assessments can be found in the Schedule of Activities in each relevant sub-protocol.

6.3. Medical History and Malignancy History

Medical, surgical, and malignancy history, including histologic confirmation of tumor, primary tumor diagnosis and recurrence dates, prior treatments, treatment dates, tumor responses, etc., should be recorded on the appropriate eCRF. Demographics, including age, sex, race, and ethnicity, will be recorded.

6.4. Archival Tumor Samples

See each sub-protocol.

6.5. Freshly Acquired Tumor Samples for Pharmacodynamic Analysis

See each sub-protocol.

6.6. Circulating Tumor DNA (ctDNA) Samples: Blood

For circulating tumor DNA (ctDNA) sample collection regimen and schedule, please refer to sub-protocols.

6.7. Physical Examination

Physical examinations will also include review of systems (neurological, chest, extremities, genitourinary, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, and skin) during screening, prior to the start of each new cycle, at EOT, and at safety follow-up. Symptom-directed physical examination, including measurement of weight and height, may be performed at other time points after screening per the Scheduled of Activities in each sub-protocol.

Patient's skin discomfort, visual disturbance, and cardiopulmonary symptoms need to be noted during physical examination. If any abnormalities arise, relevant specialist examinations should be performed in a timely manner.

6.8. Eastern Cooperative Oncology Group Status/Lansky Performance Status

The Eastern Cooperative Oncology Group (ECOG) (patients aged 16 years or older) or Lansky (patients aged less than 16 years) Status should be assessed in all patients per the Schedule of Activities in each sub-protocol (See Appendix A).

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

For patients 12 to < 18 years of age, pubertal stage will be measured according to the Tanner Stages before the start of treatment (screening) and yearly thereafter while on active treatment through sexual maturity (Marshall and Tanner 1969, Marshall and Tanner 1970). For female patients, age at menarche will be recorded.

6.10. Vital Signs

Vital signs should include the following:

- Systolic and diastolic blood pressure (BP) (For more information on normal ranges of BP by height and weight refer to Appendix H)
- Heart rate, respiratory rate, oxygen saturation, body temperature

For patients, < 18 years of age, blood pressure should be taken manually (auscultatory method) using an appropriate-sized cuff for the patient's arm dimension with feet on the floor. Care should be taken to measure blood pressure prior to other assessments and once child has been calm for a sufficient amount of time. Abnormal blood pressures should be repeated. If (automated) oscillometric methods must be used, then abnormal values should be confirmed with a manual measurement.

6.11. Ophthalmology Examination

See Sub-Protocol DAY101-102a and Sub-Protocol 102b.

6.12. Visual Symptom Assessment

See Sub-Protocol DAY101-102a and Sub-Protocol 102b.

6.13. Dermatologic Examination

A baseline dermatologic examination of the entire skin should be performed by the Investigator and/or a dermatologist. The initial examination by the Investigator/dermatologist should include a complete dermatological history of prior medications and cutaneous squamous cell carcinoma (SCC) risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior SCC, use of tanning beds, precursor lesions, and photochemotherapy for psoriasis).

Subsequent examinations should be symptom-directed and as clinically indicated and should be assessed by the Investigator and/or a consulting dermatologist for skin lesions, especially for keratoacanthomas and squamous cell carcinomas.

For each skin lesion observed, the dimensions and location on the body will be recorded. Existing lesions will be monitored throughout the study, and changes to the lesions should be recorded in the eCRF. Lesions developing during therapy that are suspected keratoacanthomas or squamous cell carcinomas will be biopsied and adequately treated; other lesions may be biopsied per the discretion of the Investigator/dermatologist. Any new or worsening skin lesions or rashes should be reported as adverse events.

Melanoma patients with clinical lesions followed for response please refer to Appendix B for additional details.

Recommended prophylactic skin care regimen and management options for rashes is available in each sub-protocol. It is recommended all patients receiving study drug follow the prophylactic skin care regimen.

6.14. Neurologic Examination

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.

6.15. Height and Bone Age

Patients 12 – 18 years (inclusive) should have changes in height compared to standard growth curves to monitor potential effects on bone growth.

Patients 12 – 18 years (inclusive) will have a bone age assessment via bone age radiograph of the left wrist during screening. Patients without epiphyseal closure at the time of screening will have a bone age left wrist radiograph performed every 6 months to monitor for the potential risk of growth retardation.

6.16. Cardiac Function

6.16.1. Electrocardiograms

Twelve-lead resting electrocardiogram (ECGs) will be performed in triplicate per the Schedule of Activities in each sub-protocol. To minimize variability, it is important that patients be in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. ECGs for each patient should be obtained from the same machine whenever possible. Any clinically significant changes in ECGs that occur during the study should be reported as AEs in the eCRF.

6.16.2. Echocardiogram/Multiple-Gated Acquisition

Echocardiogram (ECHO) or multi-gated acquisition (MUGA) will be performed per normal site protocol. The choice of ECHO or MUGA is left up to the Investigator, but the same technique should be used for each patient for each evaluation period. Any clinically significant changes in ECHO/MUGA that occur during the study should be reported as AEs in the eCRF.

6.17. Laboratory Tests

For pediatric/adolescent 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).

Routine laboratory tests will be performed locally. Special assessments such as PK will be performed centrally or as individually indicated. Additional information on the handling and processing of PK samples is provided in the separate Laboratory Manual.

6.17.1. Pregnancy Test

Urine or serum pregnancy tests are required for women of childbearing potential (surgically sterilized female patients or those who have not experienced menses for at least 2 years are not required to be tested). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If the serum pregnancy test is positive, the patient will be permanently discontinued from study treatment. Pregnancy reporting information is provided in Section 8.1.5.

6.17.2. Hematology

Hematology should include assessment of the following: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count.

6.17.3. Serum Chemistries

Serum chemistries (non-fasting) should include assessment of the following: alkaline phosphatase, albumin, alanine aminotransferase (ALT), AST, CPK, blood urea nitrogen (BUN), creatinine, creatinine clearance, glucose, lactate dehydrogenase, total and direct bilirubin, total protein, sodium, serum calcium (corrected calcium), phosphate, magnesium, and potassium. For calculated creatinine clearance, see Appendix I.

6.17.4. Coagulation Panel

Serum coagulation panel should include assessment of the following: prothrombin time (PT)/international normalized ratio (INR) and activated prothrombin time (PTT).

6.17.5. Thyroid Function Tests

Thyroid function tests should include assessment of the following: thyroid stimulating hormone (TSH) and free tetraiodothyronine (free T4). Triiodothyronine (T3) may be obtained as a reflexive test if considered necessary by the Investigator based on local practice.

6.18. Pharmacokinetic Samples: Blood

For PK sample collection regimen and schedule, please refer to sub-protocols.

6.19. Disease Assessment

6.19.1. Tumor Measurements

Disease assessment must be conducted in accordance with the Imaging Manual. Tumors will be assessed by radiographic tumor measurements using computed tomography (CT) and/or MRI (as indicated).

CT/MRI must be performed within 28 days prior to the first dose of study drug during screening. To ensure image consistency, the same imaging modalities and acquisition protocols used at screening are to be used for subsequent tumor assessments.

Investigators must conform to the CT and/or MRI acquisition requirements specified in the Imaging Manual consistently for all patients throughout the study. Disease assessments will

use RECIST version 1.1 or RANO criteria, as clinically appropriate (see Appendix B and Appendix C).

6.19.1.1. Collection of Radiographic Studies for Independent Review

Baseline screening radiographic studies and all subsequent radiographic studies will be collected and stored for independent radiological review.

Identification of radiographic findings that may affect patient management or outcomes during the course of patient participation in the study are the responsibility of the treating physician. Independent radiology review for this trial is only used to assess the objectives of the study. Any unexpected medical findings identified during subsequent independent radiologic review will not be reported back to the Investigator.

6.20. Telephone/Telemedicine Visit

The site will contact the patient or the patient's parent/legal guardian by telephone for telephonic/telemedicine visits to assess for tolerability, continuation of study drug, and whether the patient needs to return to clinic earlier than planned. The patient or the patient's parent/legal guardian should be contacted regularly to assess AE status.

6.21. Survival Status

Patients will be followed for survival status, date of progression, and subsequent anticancer therapies by telephone or any other method.

6.22. Study Drug Administration and Dosing Diary

Completion of the outpatient dosing diary will include recording of study drug dosing.

6.23. Concomitant Medication

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 eCRF.

6.24. End of Treatment Visit

EOT is defined as Day 28 (± 7 days) of the final cycle of treatment (or time of premature discontinuation of treatment). The EOT assessments and procedures will be conducted in accordance with the Schedule of Activities in the relevant sub-protocol.

6.25. Safety Follow-up Visit

Safety follow-up assessments may be performed as part of the EOT visit if the latter was performed at least 28 days after final dose of the last cycle. The safety follow-up visit may be conducted by telephone if patient is not able to return to clinic.

6.26. Long-Term Follow-up

After study treatment discontinuation, LTFU assessments will occur approximately every 3 months (± 1 month) until the patient withdraws consent for further participation, is lost to follow-up, has died, or the study is closed. For any patient who discontinues study treatment prior to disease progression, tumor assessment will progress accordingly as if on study treatment and will be requested to return to site for continued monitoring and assessment. After progression and in LTFU, the site will contact the patient or the patient's parent/legal guardian for follow-up assessments that may include subsequent anticancer therapies and survival status. LTFU may be conducted by telephone except for those patients who have not yet progressed after treatment discontinuation. For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up. The first LTFU assessment will occur 3 months (± 1 month) after the EOT visit.

6.27. Force Majeure Flexibility

With the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the impact of coronavirus disease 2019 (COVID-19) on the health-care system, the Sponsor of this study recognizes the need for flexibility in ensuring access to therapy. This need has been clearly elucidated in the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (FDA-2020-D-1106) and the EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (Version 3, 28/04/2020). While every effort should be made to follow the timing of study visits and procedures as closely as possible, the Sponsor may introduce flexibility in the nature and timing of visits. Changes may include using home health-care visits, telemedicine visits, local imaging, and distribution of multiple cycles of investigational product (or shipping investigational product to a patient's residence).

If such flexibility needs to be implemented for the safe conduct of this study, the Sponsor will notify sites of what procedures may be delayed or provide flexibility in how data are collected. As potential impacts to the health-care system may not be uniform through all regions where the Sponsor is conducting this study, guidance will be informed by worldwide regulatory authority guidance and local competent and ethical authorities and may vary from site to site. Changes to timing and procedures will be communicated by the Sponsor through an official memo and training.

7. PLANNED ANALYSES

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock for each sub-protocol. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Any deviations in the planned analysis as stated in the protocol will be delineated in the SAP. Any deviations from the SAP will be reported in the clinical study report.

7.1. Analysis Populations

The populations for analysis are defined in Table 7.

Table 7: Population Definitions

Population	Description
Efficacy	All patients who received at least 1 dose of study drug and have measurable disease as determined by the Investigator at baseline and have at least 1 follow-up imaging or radiographically confirmed progressive disease prior to the first imaging timepoint (FAS)
Safety	All patients enrolled in the study who received at least 1 dose of study treatment (SAS)
DLT	Patients enrolled in a safety run-in cohort, received at least 1 dose of study treatment, and completed 75% of dosing in Cycle 1, unless discontinued for toxicity

Abbreviations: DLT, dose-limiting toxicity; FAS, Full Analysis Set; SAS, Safety Analysis Set.

7.2. Determination of Sample Size

For methods related to determination of sample size, refer to specific sub-protocols. Additional patients will be enrolled to account for any patients who are lost to follow-up or have no follow-up imaging.

7.3. Statistical Methods

The SAP will be produced individually for each sub-protocol prior to analysis.

7.3.1. Efficacy Analyses

The efficacy analyses will be performed on the full analysis set (FAS) population which includes all patients who received at least 1 dose of study drug and have measurable disease as determined by the Investigator at baseline and have at least 1 follow-up imaging or radiographically confirmed progressive disease prior to the first imaging timepoint.

ORR as assessed by the proportion of patients with the best overall confirmed response of CR or PR, according to the appropriate tumor response criteria as assessed by Investigator will be calculated and an exact CI will be calculated. DOR in patients with best overall response of CR or PR as determined by the treating Investigator defined as from time of first tumor response to progression or date of data analysis, whichever occurs earlier will be calculated. PFS is defined as the time from the date of the first dose of study drugs to the first occurrence of disease progression according to the appropriate tumor response criteria as

assessed by Investigator, or death from any cause, whichever occurs earlier. OS is defined as the period from the date of the first dose of study drugs until the date of death from any cause. Kaplan-Meier curves will be plotted for DOR, PFS, and OS. TTR in patients with best overall response of CR or PR will be determined by the treating Investigator from the initiation of study treatment to the date of first response. The timepoint for the analysis of response for Phase 2 studies' primary efficacy objective will be when all patients have a minimum of 6 months of follow-up.

7.3.2. Safety Analyses

Safety will be assessed by clinical review of all relevant parameters, including AEs, SAEs, AESIs, laboratory values, and vital signs. Unless specified otherwise, the safety analyses will be conducted for the Safety Analysis Set defined in Section 7.1.

The reported AE term will be assigned a standardized Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or later, and adverse event severity will be graded according to National Cancer Institute (NCI) CTCAE v5.0.

Treatment-emergent adverse events will be tabulated according to MedDRA by system organ class, high level terms, and preferred terms and will be include the following categories: frequency of AEs overall, by grade, relationship to study treatment, time-of-onset, duration of the event, duration of resolution, and any concomitant medications administered. A listing of TEAEs resulting in study drug discontinuation will be provided. For reporting purpose, treatment-emergent adverse event is defined as new or worsening adverse events occurring on or after the first dose of study drug is administered until the clinical cutoff date. All safety analyses of adverse events will also include all adverse events with onset on or after the first study drug treatment until the data cutoff date.

7.3.2.1. Deaths

All deaths on study should be reported and recorded. Deaths will be reported in a patient listing and will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

7.3.2.2. Laboratory Values

Laboratory values will be assigned toxicity grades when available using the NCI CTCAE, version 5.0 or later. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation. Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) and other safety parameters as deemed appropriate will be presented for all scheduled measurements over time. Mean laboratory values over time will be presented for key laboratory parameters.

7.3.2.3. Vital Signs

All patients will have pretreatment baseline vital signs and pre-dose measurements as described in the Schedule of Activities in the relevant sub-protocol. The results for each vital sign will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by time point in the same manner described for laboratory values. For these analyses, the minimum, maximum, average, and last post-baseline value will be determined relative to the baseline vital sign measurements only.

7.3.2.4. Concomitant Medications

Prior and concomitant medications will be coded to the generic term using the current version of the World Health Organization (WHO) Drug Dictionary and listed by patient.

7.3.3. Pharmacokinetic Analyses

Plasma concentrations of DAY101 and other therapies (as applicable based on sub-protocol) will be determined with validated bioanalytical methods. Plasma concentrations will be analyzed at specified time points in order to generate PK parameters as appropriate and will be described in more detail in the sub-protocol(s). Summary statistics will be generated as appropriate.

8. ADVERSE EVENTS

8.1. Adverse Events, Adverse Events of Special Interest, and Serious Adverse Events

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, AESI, or SAE and remain responsible for following up AEs that are serious, considered events of special interest, considered related to the study intervention or study procedures, or caused the patient to discontinue DAY101 or combination partner.

All AEs, whether reported by the patient or the patient's parent/legal guardian or noted by study personnel, will be recorded in the patient's medical record on the Adverse Event eCRF.

See Appendix G for instructions on collection, assessing, and reporting of AEs.

8.1.1. Time Period and Frequency for Collecting Adverse Event, Adverse Events of Special Interest, and Serious Adverse Event Information

Report all SAEs deemed related to protocol-mandated procedures from the signing of informed consent through to start of treatment with DAY101 or combination partner, whichever is administered first.

Report all AEs, AESIs, including SAEs, from the start of treatment until 30 days after the last dose of DAY101 or combination partner, whichever was administered last.

For patients who screen fail or are enrolled but do not receive study drug, the reporting period for SAEs ends 30 days after the last procedure (e.g., screening procedure).

Table 8: Summary of AE Collection Periods

Time Period	AE Collection
ICF signature to start of study drug	Protocol/procedure-related SAEs only
Start of study drug to 30 days after last study drug dose (DAY101, additional study treatment, whichever was administered last)[a]	All AEs, AESIs, and SAEs
Beyond 30 days after last study drug dose (DAY101, additional study treatment, whichever was administered last)	Any SAEs or AESIs related to study drug

Abbreviations: AE, adverse event; AESI, adverse event of special interest; ICF, informed consent form; SAE, serious adverse event.
[a] See Section 8.1.3 for follow-up of AEs. If a patient begins a new anticancer therapy, the AE reporting period for non-SAEs and SAE/AESIs not related to study drug ends at the time the new treatment is started.

Report and record all SAEs to the Sponsor or designee within 24 hours following the Investigator's knowledge of the events, as indicated in Appendix G. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of their being available.

Non-serious AESIs should be reported in the same manner as reporting of SAEs. In addition, for both serious and non-serious AESIs, the appropriate targeted questionnaires should be submitted to the Sponsor with the SAE report or as soon as possible.

If the Investigator learns of any SAE and/or AESI, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.1.2. Method of Detecting Adverse Events, Adverse Events of Special Interests, and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs, AESIs, and SAEs and the procedures for completing and transmitting SAE and non-serious AESI reports are provided in Appendix G.

Care will be taken not to introduce bias when detecting AEs, AESIs, and/or SAEs. Open-ended and nonleading verbal questioning of the patient or the patient's parent/legal guardian is the preferred method to inquire about AE occurrences.

8.1.3. Follow-up of Adverse Events, Adverse Events of Special Interests, and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up. Further information on follow-up procedures is provided in Appendix G.

Non-serious AESIs should be followed-up in the same manner as SAEs.

If a patient begins a new anticancer therapy prior to 30 days post study drug EOT, the AE reporting period for non-SAEs and SAE/AESIs not related to study drug ends at the time the new treatment is started.

8.1.4. Regulatory Reporting Requirements for Any SAEs and Non-Serious AESIs Occurring During this Study Must Be Reported as Follows:

- Prompt notification of an SAE or AESI by the Investigator to the Sponsor is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of a study intervention under clinical investigation are met. Any SAEs (including Serious AESIs) must be reported to the Sponsor via email at [redacted] within 24 hours. Non-serious AESI's should be reported using the same processes and timelines as SAEs.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with countryspecific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements. A non-serious AESI does not require expedited reporting to any regulatory health authority or agency.

8.1.5. Pregnancy or Combination Partner

There is no relevant clinical experience with DAY101 (as a single agent or in combination) in pregnant or lactating female patients, and animal reproductive studies have not been performed. Women of childbearing potential must have a negative pregnancy test prior to enrollment because of the potentially dangerous effects of the preparative chemotherapy on the fetus. This experimental therapy should not be administered to pregnant women or women who are breastfeeding.

- Details of all pregnancies in female patients and female partners of male patients will be collected for pregnancies occurring after the start of study intervention until 6 months after completing DAY101.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix F.
- If a lactation case is reported, the Investigator should inform the Sponsor within 24 hours of learning of the lactation case and should follow the procedures outlined in Appendix F.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

In addition to reporting any pregnancies or lactation cases occurring during the study, Investigators should monitor for pregnancies or lactation cases that occur after the last dose of DAY101 through 6 months for female patients and for 6 months for female partners of male patients.

8.1.6. Death Events

Deaths occurring during the AE reporting period, regardless of attribution to DAY101 or combination partner will be recorded as a serious AE and expeditiously reported to the Sponsor. This includes death attributed to the progression of malignant disease.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical condition on the Adverse Event eCRF and SAE report form, as applicable. If the cause of death is unknown and cannot be ascertained at the time or reporting, then “unexplained death” should be recorded on the Adverse Event eCRF and SAE reporting form, as applicable.

8.2. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established to oversee the safety aspects of the study and to render dose safety decisions as applicable based on sub-protocol (see Section 8.2.1).

8.2.1. Risk Management

An independent DMC will also be commissioned to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study and to review available efficacy data. The independent DMC will be composed of experts in the field of oncology, as well as biostatistics, and clinical trial conduct. Members of the independent DMC will not be associated with the conduct of the study, except in their role on the independent DMC. The Sponsor will also designate an independent biostatistical team not affiliated with the project to prepare and provide study data to the independent DMC. The independent DMC will meet periodically to review ongoing efficacy and safety data. Timing of the first independent DMC meeting will be enrollment driven, and subsequent meetings will occur approximately every 3 months (or longer based on patient accrual) to review safety across the DAY101-102 master study and sub-protocols. Complete details regarding the composition and governance of the independent DMC, independent DMC responsibilities, authorities, and procedures will be outlined in a separate independent DMC Charter. The independent DMC responsibilities, authorities, and procedures will be documented in a separate charter.

8.2.2 Continuous Review of Safety Data

The eCRF used for this study allows real-time tracking of safety data. Safety data review will be reviewed by the Sponsor or designee regularly, and safety signals or trends will be escalated to the DMC accordingly.

Serious adverse events will be reported within 24 hours to the Sponsor's safety team by email and be subject to a second assessment by the Sponsor's safety physician.

8.3. Stopping Rules

AEs and SAEs are expected to occur frequently in this study, based on the patient population being accrued and on the nature of the advanced malignancies under study. SAEs will serve as the basis for pausing or prematurely stopping the study. Unexpected SAEs that are assessed as related to DAY101 or combination partner will continuously be reviewed to determine any necessary pausing or stopping of the study. The study may be paused for enrollment if any patient experiences any of the following events:

- Life-threatening (Grade 4) toxicity attributable to DAY101 or combination partner that is unexpected and unmanageable (i.e., does not resolve to Grade 3 or lower within 7 days)
- Death related to DAY101 or combination partner

Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the Sponsor or at the recommendation of the DMC. Decisions to pause enrollment or terminate the study will be communicated promptly to Investigators,

IRBs/IECs, Institutional Biosafety Committees (if applicable), and appropriate regulatory authorities.

During any temporary enrollment hold, no new participants can be enrolled, nor can any newly enrolled participants start study intervention. Participants who have already started study intervention may continue treatment only if the benefit/risk assessment for the participant is judged to be positive by the Investigator in consultation with the Sponsor.

8.4. Grading and Intensity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, version 5. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening/debilitating, or fatal, as defined below.

Table 9: NCI CTCAE Definitions of Severity for Adverse Reactions

Toxicity	Grade / Details
Grade 1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; no interventions required (an event that is usually transient in nature and generally not interfering with normal activities)
Grade 2	**Moderate**; minimal, local, or noninvasive intervention indicated; some limitation of activities (an event that is sufficiently discomforting to interfere with normal activities)
Grade 3	**Severe or medically significant but not immediately life-threatening**; hospitalization or prolongation of hospitalization required; disabling; limitation of patient's ability to care for him/herself (an event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity)
Grade 4	**Life-threatening consequences**; urgent intervention required (an event that puts the patient at immediate or potential risk of death, requires hospitalization, or which drastically impacts a patient's well-being)
Grade 5	**Death related to adverse event** (fatal)

Abbreviations: NCI CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.

8.5. Relationship to Study Drug

The Investigator is required to assess the causality/relationship between each AE and the study drug as not related or related and record the assessment on the source documents and in the CRF AE page. Medical judgment should be used to determine the likely relationship of the AE to the study drug considering all relevant factors including (but not limited to) relevant history, concomitant medical condition, and concomitant medications. Determination should be based on assessment of temporal relationships, biologic plausibility, association (or lack of association) with underlying disease, and presence (or absence) of a more likely cause.

- **Related:** A causal relationship between medicinal product and an AE is at least a reasonable possibility. The AE cannot reasonably be explained by the patient's clinical state, concomitant medical condition or concomitant therapies, and a temporal relationship exists between the event onset and administration of the study drug.
- **Not Related:** It is plausible that the AE has an etiology other than the study drug (e.g., preexisting condition, underlying disease, concomitant medical condition, or concomitant medication).

8.6. Serious Adverse Event Follow-up

For all SAEs occurring during the study, the Investigator must submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course until the SAE has resolved, the condition stabilizes or is deemed chronic (in the case of persistent impairment), the patient or the patient's parent/legal guardian withdraws consent for further follow-up, or the patient dies.

For non-serious AESIs reported to the Sponsor, the Investigator should submit the appropriate follow-up reports regarding the patient's subsequent course similar to what is required for SAE follow-up.

9. STUDY ADMINISTRATION

9.1. Regulatory and Ethical Considerations

9.1.1. Regulatory Authority Approval

This study will be conducted in accordance with the standard of Good Clinical Practices (GCP), an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. All applicable country and local regulations will also be observed. Compliance with these standards provides assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles in the Declaration of Helsinki, and that the clinical study data are credible.

9.1.2. Ethics Approval

It is the responsibility of the Investigator to ensure that the appropriate IRB/ Research Ethics Board (REB)/IEC/ Human Research Ethics Board (HREC) has reviewed and approved this protocol prior to initiating the study. The Investigator must provide the Sponsor or Sponsor's representative with current and revised IRB/REB/IEC/HREC membership rosters that include the members' occupations and qualifications or provide a copy of the US Department of Health and Human Services Assurance Number.

The IRB/REB/IEC/HREC must also review and approve the clinical site's ICF, pediatric assent form, other written information provided to the patient, and all advertisements that may be used for patient recruitment. The Investigator will provide the study monitor with copies of these documents and of dated IRB/REB/IEC/HREC approval(s) prior to the start of the study.

The IRBs/REBs/IECs/HREC are required to determine whether child assents are appropriate for all studies that include pediatric patients. The IRB/REB/IEC/HREC may opt to waive assent if the patients are not capable of understanding (e.g., based on level of intellectual development or maturity) or if the study is in the best interest of the patient (i.e., strong possibility of benefit and no other alternatives are available). If an IRB/REB/IEC/HREC chooses to waive assent, this must be documented in the IRB/REB/IEC/HREC approval letter.

If the protocol or the ICF or pediatric assent form is amended during the study, the Investigator is responsible for ensuring that the IRB/REB/IEC/HREC has reviewed and approved these amended documents. Approval of the amended documents must be obtained from the IRB/REB/IEC/HREC before implementation and before new patients are consented to participate in the study using the amended version of the ICF/pediatric assent form. The Investigator must provide the Sponsor with the dated IRB/REB/IEC/HREC approval of the amended documents as soon as available.

9.1.3. Patient Informed Consent and Pediatric Assent

The Investigator and designated site staff who will perform the consent/assent process are responsible for knowing country-specific regulations and other local requirements with regards to child assent to ensure that the assent process is conducted in accordance with those requirements. Prior to study entry, the Investigator or designee will explain the nature,

purpose, benefits, and risks of participation in the study to each patient and the patient's legally acceptable representative, legal guardian, or impartial witness. Written informed consent and pediatric assent, where applicable, must be obtained prior to the patient's entering the study (before initiation of any study-related screening procedure). In pediatric cases, where applicable and according to local regulations, both parents may be required to sign informed consent. Sufficient time will be allowed to discuss any questions raised by the patient. The ICF/pediatric assent form, which will contain all US federally -required elements, all International Council for Harmonisation (ICH) -required elements, and Health Insurance Portability and Accountability Act authorization information in a language that is understandable to the patient, must be signed by all patients, or by the patient's legal representative. The process of obtaining the ICF and pediatric assent form, where applicable, will be in compliance with all applicable local and country regulations and ICH requirements.

The pediatric assent form must have a date and signature line for the child. State laws differ in their requirements for patients who have not reached the legal age of majority and IRBs/REBs/IECs/HRECs are responsible for following their local regulations. Use of an assent is not a substitute for parental permission. Parents/guardians must receive a full ICF to review and sign.

If the ICF and pediatric assent form, where applicable, is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to IRB/REB/IEC/HREC approval of the amended form. The clinical site must use the amended ICF/pediatric assent form for all new patients and repeat the consent/assent process with the amended form for any ongoing patients.

An initial ICF (for adult patients or parent/guardian of child/adolescent patients) and pediatric assent form (for child/adolescent patients, as applicable) will be provided to the Investigator to prepare the ICF and assent documents to be used at the Principal Investigator's site. The sample ICFs/pediatric assent forms prepared by the Sponsor are provided in the Study Manual.

9.1.4. Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB/REB/IEC/HREC of progress of the study and notify the IRB/REB/IEC/HREC of study closure. The Investigator must also provide the Sponsor with copies of all IRB/REB/IEC/HREC correspondence that relate to study approvals, updates, or changes. The Investigator is also responsible for forwarding to the IRB/REB/IEC/HREC reports of any SAEs from other studies conducted with the same investigational product that were provided by the Sponsor.

9.2. Data Management

Data will be recorded at the site on source documents and reviewed by the Sponsor's site monitor, who will verify data recorded in the eCRFs with source documents, during periodic visits. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system. The eCRFs will be considered complete when all missing,

incorrect, and/or inconsistent data have been accounted for. Additional instructions on eCRF completion are provided in the electronic data capture (EDC) manual.

All eCRFs must be reviewed and signed by the Investigator.

9.3. Study Monitoring

Prior to the start of the study, the Sponsor's monitor or designee will contact the clinical site to discuss the protocol and data collection procedures and conduct applicable training of site personnel. The Sponsor and its designees will also periodically contact the clinical site during the conduct of the study (which will include remote and on-site visits) in accordance with applicable regulations and GCP. During these contacts, the monitoring activities will include the following:

- Checking and assessing the progress of the study
- Reviewing study data collected to date for completeness and accuracy
- Conducting source document verifications by reviewing each patient's eCRF against source documents
- Identifying any issues and addressing resolutions
- Recording and reporting protocol deviations not previously reported to the Sponsor
- Confirming that SAEs and non-serious AESIs have been properly reported to the Sponsor and submitted to the IRB/REB/IEC/HREC if appropriate

These activities will be done to verify that the data are authentic, accurate, and complete; that the safety and rights of the patient are being protected; and that the study is conducted in accordance with the currently approved protocol, GCP, and all applicable regulatory requirements. Additionally, to ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or designee may conduct a quality assurance audit.

9.4. Termination

Upon completion of the study, the following activities, when applicable, must be conducted by the study monitor and the Investigator:

- Submission of all study data to the Sponsor
- Completion of all data clarifications and/or resolutions
- Reconciliation and final disposition of investigational product
- Review of site study files for completeness

In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator, and will also inform the IRB/REB/IEC/HREC with the reasons for the action. In the event of prematurely termination, all study data must be submitted to the Sponsor. In addition, the clinical site must document final disposition of all unused investigational product in accordance with the Sponsor's procedures.

9.5. Records Retention

Patient records, source documents, monitoring visit logs, investigational product inventory, regulatory documents, and other correspondence pertaining to the study must be maintained in the appropriate site study files according to ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified immediately by telephone or e-mail and the notification confirmed in writing if a custodial change occurs.

9.6. Confidentiality of Information

Patient names will remain confidential and will not be supplied to the Sponsor or its designee. The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

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Appendix A: Eastern Cooperative Oncology Group (ECOG) Performance Status and Lansky Performance Score

Table 10: ECOG Performance Status

ECOG Performance Status[a]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confirmed to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

[a]As published in *Am. J. Clin. Oncol*. (Oken et al., 1982)

Table 11: Lansky Performance Score (< 16 years old)

Score	**Lansky Description**
100	Fully active, normal
90	Minor restrictions in strenuous physical activity
80	Active, but tired more quickly
70	Greater restriction of play *and* less time spent in play activity
60	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50	Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bed bound; needing assistance even for quiet play
20	Sleeping often; play entirely limited to very passive activities
10	Doesn't play; doesn't get out of bed
0	Unresponsive

(Lansky et al. 1987)

Appendix B: Response Evaluation Criteria in Solid Tumors: Revised RECIST Guideline (Version 1.1)

A revised RECIST guideline (version 1.1) was developed by the RECIST Working Group (Eisenhauer et al. 2009, Table 12). Notable changes are highlighted below:

- Number of lesions required to assess tumor burden for response determination has been reduced from a maximum of 10 to a maximum of 5 total (and from 5 to 2 per organ, maximum).
- Nodes with a short axis of 15 mm are considered measurable and assessable as target lesions. Nodes that shrink to <10 mm short axis are considered normal.
- In addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well.

MEASURABILITY OF TUMOR LESIONS AT BASELINE

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) and 20mm by chest X-ray
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Special considerations regarding lesion measurability of bone lesions, cystic lesions, and lesions previously treated with local therapy can be found in RECIST version 1.1 and are briefly summarized as follows:

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.
- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤5mm.

MRI is also acceptable in certain situations (e.g. for body scans).

Use of ultrasound, endoscopy, laparoscopy, biomarker, and cytology/histology are not recommended for additional details refer to RECIST v1.1.

TUMOR RESPONSE EVALUATION

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

A maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’.

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of Best Overall Response

The best overall response is determined once all the data for the patient is known. Guidance on the determination of tumor response at each time point is provided in Table 12. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). Guidance on the determination of best overall confirmed response is provided in Table 13.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document objective disease progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated, i.e. biopsied if accessible.

Table 12: Overall Assessment by RECIST 1.1 at Each Time Point

Target Lesion	Non-Target Lesions	New Lesions	Overall Response
CR	CR or none at BL	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not all evaluated (NE)	No	PR
PR	Non-PD or NE or none at BL	No	PR
SD	Non-PD or NE or none at BL	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
None identified at BL	CR	No	CR
None identified at BL	Non-CR/Non-PD	No	Non-CR/Non-PD
None identified at BL	Not all evaluated	No	NE
None identified at BL	PD	Yes or No	PD
None identified at BL	None identified at BL	Yes	PD

Abbreviations: BL, baseline; CR, complete response; NE, not all evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

Table 13: Best Overall Assessment by RECIST 1.1

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Confirmed Overall Response
CR	CR	CR
CR	PR	PR[a], SD, PD
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: Abbreviations: CR, complete response; NE, not all evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix C: Response Assessment in Neuro-Oncology (RANO) Criteria for Primary CNS Malignancies

The RANO criteria (Wen et al. 2017; Table 14) were developed to evaluate efficacy of investigational agents in glioblastoma clinical trials and have been more broadly used for lower grade primary CNS malignancies. These criteria were developed in part to address issues faced when assessing some lesions based on MacDonald criteria, particularly lesions with central necrosis and with a T2 component.

Table 14: RANO Response Criteria Incorporating MRI and Clinical Factor

RESPONSE CATEGORY	CRITERIA
Complete Response	• Disappearance of all measurable and non-measurable enhancing disease • Stable or improved nonenhancing FLAIR/T2 lesions • No new lesions • Clinically stable or improved with no reliance on corticosteroids (except for physiological replacement)
Partial Response	• ≥ 50% decrease from baseline of all measurable enhancing lesions • No progression of non-measurable disease • Stable or improved nonenhancing FLAIR/T2 lesions • No new lesions • Clinically stable or improved, with stable or reduced corticosteroids compared to baseline
Progressive Disease	• ≥ 25% increase from baseline in enhancing lesions despite stable or increasing steroid dose • Significant increase in nonenhancing FLAIR/T2 lesions not attributable to other non-tumor causes • Any new lesions • Clinical deterioration no attributable to other non-tumor causes and not due to steroid decrease
Stable Disease	• Does not meet other criteria for response or progression • Stable nonenhancing FLAIR/T2 lesions • Clinically stable with stable or reduced corticosteroids compared to baseline

Abbreviations: FLAIR/T2, T2-weighted fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; RANO, Response Assessment in Neuro-Oncology.

A measurable lesion is evaluated by contrast-enhancing MRI and:

- Has clearly defined margins
- Is visible on 2 or more axial slices, preferably < 5 mm thick
- Is at least 10 mm in size if slice thickness is < 5 mm (or 2× slice thickness if > 5 mm)
- Does not measure a cystic cavity

Non-measurable lesions are those that do not fit the criteria above, and specifically lesions that are cystic, necrotic, or include a surgical cavity should not be considered measurable.

Measurements are calculated by summing the products of perpendicular diameters of all measurable enhancing lesions.

If there are multiple contrast-enhancing lesions, a minimum of the 2 largest lesions should be measured. However, emphasis should be placed on selecting lesions that allow reproducible repeated measurements. For patients who have multiple lesions for which only 1 or 2 are increasing in size, the enlarging lesions should be considered the measurable lesions for evaluation of response.

Appendix D: Specimen and Data Use

Research Uses of Tissue and Clinical Data

Any leftover tissue samples will be banked for future analyses that are not yet available. Clinical data and tissue samples, independently and together, will be used for nontherapeutic research that advances the diagnosis, evaluation, etiology, prevention, and outcome improvement of nervous system diseases. Research on tissue samples may include detailed genetic and molecular analysis and cell line development. In general, these findings will be linked to clinical care and outcome to maximize research findings. Studies may include tumor biology studies, biomarker identification studies, drug target studies, genomics and proteomics studies, genetic susceptibility studies, drug development efforts, epidemiological studies, and outcomes studies. Use of leftover tissue samples is optional and can only be done with the consent of the patient.

Retrospective analysis on clinical data performed outside of prospective formal clinical trial data will be linked with outcomes to create research findings and provide preliminary data to support further investigations.

For a comprehensive list of research use of tissue and clinical data, see Appendix E.

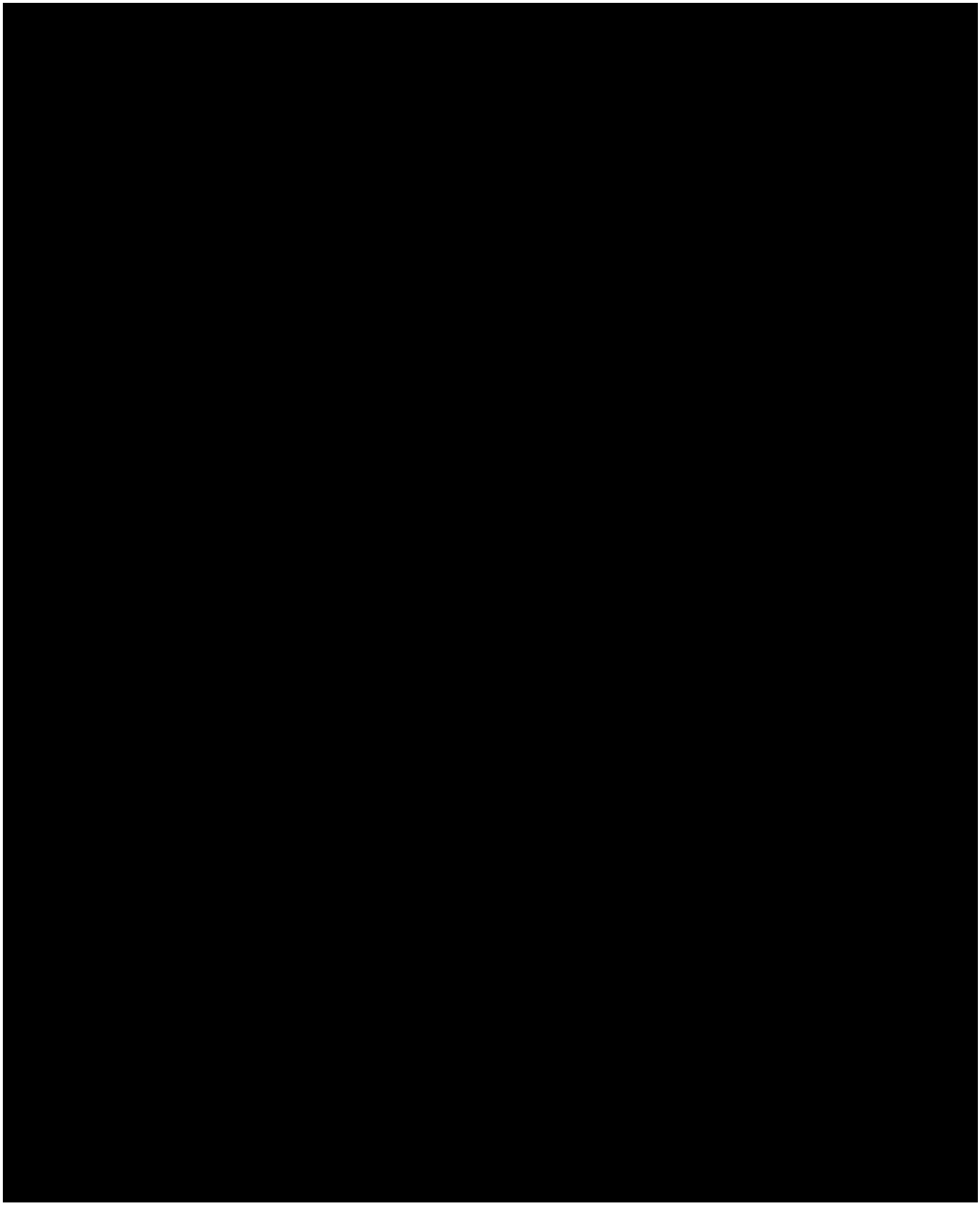
Commercial Uses of Tissue and Clinical Data

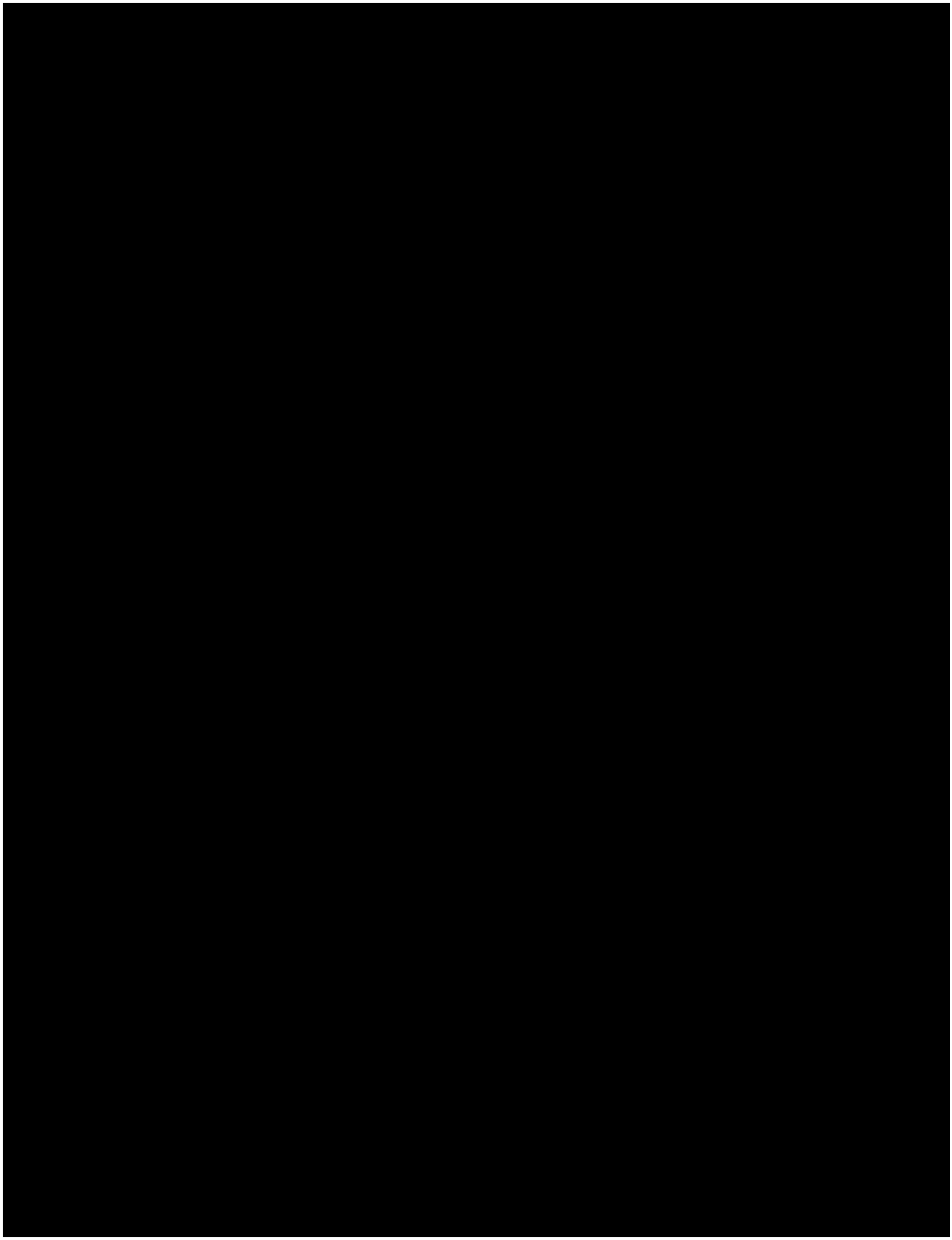
Tissue samples collected and/or stored in the bank may be made available to commercial or corporate scientific collaborators only as part of a scientific collaboration. Derivative products from the patient tissues including cell lines, diagnostics tests, or other items may arise from study of these tissues. Patients will not have any ownership or financial benefit from their tissue samples and derivatives.

Uses That May Affect Determination of Treatment (Clinical Care) and/or Eligibility In Clinical Trials

In rare circumstances, findings from tissue testing may be clinically relevant and affect treatment decisions. All test results communicated back to the patient's treating clinician and/or placed into the patient's medical record must be CLIA compliant. If the testing is first done in a laboratory that does not meet these criteria, yet the results are felt to be clinically significant, the testing will be repeated in a CLIA environment prior to informing the patient's clinician and/or placement in the patient's medical record. The patient's treating clinician is responsible for treatment decisions including whether and how to inform the patient of any results.

Appendix E: List of Research Uses of Tissue, Plasma and Clinical Data





Appendix F: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered to be fertile following menarche and until becoming postmenopausal, unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBPs:

- Premenarchal
- Premenopausal woman with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.

Contraception Guidance:

Male patients are not allowed to donate sperm during the course of this study or within 180 days after receiving their last dose of study drug.

Female and male patient of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug(s) and for 180 days after the last dose of study drug(s) by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use two acceptable methods of contraception in which one method must be a barrier (a condom is preferred) in addition to one of the highly effective contraception methods described below during heterosexual activity.

Acceptable methods of highly effective contraception methods with a failure rate of less than 1% per year are‡:

- Combined estrogen- and progestogen-containing hormonal contraception associated with inhibition of ovulation given PO, intravaginally, or transdermally
- Progestin-only hormonal contraception associated with inhibition of ovulation given PO, by injection, or by implant

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion or ligation
- Vasectomized partner

† In the context of this protocol, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period specified above. Periodic abstinence (calendar, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not acceptable methods of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not quality as an acceptable method of contraception for subjects participating at sites in this country/region.

Collection of Pregnancy Information

Male Patients With Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive DAY101.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the patient's pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 months beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.1.5. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue study intervention.

Appendix G: Adverse Events. Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Adverse Event Definition
• An adverse event (AE) is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. • The Investigator is responsible for ensuring that any AEs observed by the Investigator or reported by the patient are recorded in the patient's medical record.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). **In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, require therapy, or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.** If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin > 5 × upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event electronic Case Report Form (eCRF). • Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition • New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. Nonetheless, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfill the definition of an AE or SAE. • The term "disease progression" or "progressive disease" should not be reported as an AE, rather, report the specific malignancy as the AE term.

Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)
Non-serious adverse events of special interest should be reported by the Investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 8.1.4 for reporting instructions). Adverse events of special interest for this study include the following: 1. Rhabdomyolysis 2. Ventricular Arrhythmias 3. Intra-tumoral hemorrhages 4. Secondary primary malignancies 5. Ocular toxicities
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition • Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study participation (e.g., port placement) • Unplanned medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social, logistical, and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Events that require an escalation of care when the patient is already hospitalized should be recorded as an SAE. Examples of such events include movement from routine care in the hospital to the intensive care unit or if that event resulted in a prolongation of the existing planned hospitalization.
- Hospitalization for conditioning chemotherapy, infusion, and monitoring as required by the protocol and elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Planned admissions to hospital for administration of DAY101/additional therapies or other protocol-mandated procedures do not qualify as serious unless a new AE occurs that results in prolongation or meets any of the other "serious" criteria.

d. Results in persistent disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE, AESI, and/or SAE

AE, AESI and SAE Recording

- When an AE, AESI/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE, AESI /SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor in lieu of completion of the AE, AESI /SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Sponsor.
- **The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.** Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE, AESI /SAE (e.g., record liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). In addition, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause (e.g., if diarrhea is known to have resulted in dehydration, then it is sufficient to record only diarrhea as an AE on the eCRF).

Assessment of Causality

- The Investigator and Sponsor is obligated to assess the relationship between study intervention (DAY101/additional therapies) and each occurrence of each AE, AESI /SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information for marketed products in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor's Drug Safety Group. **However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's Drug Safety Group or designees.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when Sponsor determines regulatory reporting.

Follow-up of AEs, AESIs, and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's Drug Safety Group or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health-care professionals. • If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings, including histopathology, as applicable. • The Investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information, and should submit follow-up on non-serious AESIs in a similar manner.

Reporting of SAEs and AESIs (serious and non-serious)

SAE/AESI Reporting to Sponsor via the SAE Report and AESI Targeted Questionnaire Forms
The Investigator is responsible for ensuring that AEs are monitored and reported. See Section 8.1.1 for greater details regarding the AE, AESI, and SAE reporting periods. • Report SAEs and non-serious AESIs by completing the paper SAE form (see next section) in order to report the event within 24 hours. • For all AESIs (serious and non-serious), the applicable AESI targeted questionnaire form should be submitted with the SAE form or as soon as possible • Contacts for SAE reporting can be found in the Study Manual. • In rare circumstances and in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE Report Form within the designated reporting time frames.

Appendix H: Blood Pressure by Height and Age

The tables for normal blood pressure by height and age are included in this appendix. In order to use these tables, note that the height percentile is determined by the standard growth charts. The child's measured systolic and diastolic blood pressure (BP) is compared with the numbers provided in the table (boys or girls) for age and height percentile.

- The child is normotensive if BP is below the 90th percentile.
- If the child's BP (systolic or diastolic) is at or above the 95th percentile, the child may be hypertensive, and repeated measurements are indicated.
- BP measurements between the 90th and 95th percentiles are high normal and warrant further observation and consideration of other risk factors.

Standards for systolic and diastolic BP for infants younger than 1 year are available in the second task force report. Recently, additional data have been published.

Source: DHHS, PHS, NIH, National Heart, Lung, and Blood Institute. Update on the Task Force Report (1987) on High Blood Pressure in Children and Adolescents: A Working Group Report from the National High Blood Pressure Education Program. NIH Publication 96-3790; 1996; 7-9.

The entire NIH document can be viewed at:
http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf

Blood Pressure Levels for Boys by Age and Height Percentile*

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90

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Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Blood Pressure Levels for Girls by Age and Height Percentile*

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88

Age (Year)	BP Percentile ↓	Systolic BP (mmHg) ← Percentile of Height →							Diastolic BP (mmHg) ← Percentile of Height →						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Appendix I: Serum Creatinine Clearance Calculation

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units) in adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the isotope dilution mass spectrometry (IDMS) traceable Modification of Diet in Renal Disease (MDRD) Study equation.

This CKD-EPI equation calculator should be used when S_{cr} is reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m² are desired.

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]

Where:

- S_{cr} is serum creatinine in mg/dL,
- κ is 0.7 for females and 0.9 for males,
- α is -0.329 for females and -0.411 for males,
- min indicates the minimum of S_{cr}/κ or 1, and
- max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m² BSA, which is an accepted average adult surface area.

The GFR estimate should be calculated by CKD-EPI equation using the Merck Manual Calculator:

https://www.merckmanuals.com/professional/multimedia/clinical-calculator/glomerular-filtration-rate-estimate-by-ckd-epi-equation

Appendix J: Body Surface Area (BSA) Calculation

Body Surface Area (BSA) will be calculated using the Mosteller Method*:

BSA (m^2) = (height (cm) × weight (kg)/3600)^{½}

Also expressed as:

BSA (m^2) = square root of (height (cm) x weight (kg)/3600)

*Mosteller RD. Simplified calculation of body surface area. N Engl J Med. 1987;317:1098.