Protocol

Study ID: 213406

Study Official Title: A Phase 1, Multicentre, Open-Label, Dose-Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients With Recurrent or Refractory Solid Tumours

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TITLE PAGE

MASTER PROTOCOL

Protocol Title:	A PHASE 1, MULTICENTRE, OPEN-LABEL, DOSE ESCALATION AND COHORT EXPANSION STUDY OF NIRAPARIB AND DOSTARLIMAB IN PAEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMOURS
Protocol Number:	213406 Amendment 05
Compound Number or Name:	Niraparib (GSK3985771), Dostarlimab (GSK4057190A)
Brief Title:	Dose Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Participants With Solid Tumours
Study Phase:	Phase 1
Sponsor Name and Legal Registered Address:	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Medical Monitor Name and Contact Information:	Contact Information can be found in the local study contact information document
Sponsor Signatory:	Nidale Tarek, MD Senior Medical Director Synthetic Lethality, GSK
Regulatory Agency Identifying Number(s):	EudraCT Number: 2020-002359-39 EU CT: 2024-511071-16
Approval Date:	12 Dec 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date
Amendment 05	12 Dec 2024
Amendment 04 GBR-1	08 August 2024
Amendment 04	23 May 2024
Amendment 03	20 July 2022
Amendment 02	23 November 2020
Amendment 01	16 October 2020
Original Protocol	12 May 2020

Amendment 05 (12 Dec 2024)

Overall rationale for the current Amendment:

Protocol Amendment 05 is a substantial amendment that aligns Protocol Amendment 04 with all aspects of the UK-specific Protocol Amendment 04 GBR-1, resulting in a single global amendment. Additional changes include an update of the sponsor's legal registered address plus administrative and editorial updates and clarifications for study conduct.

A general description and brief rationale(s) for key changes are provided in the Table 2 below. The synopsis was also updated to align with the changes in the protocol body, where applicable.

Table 2 List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Title Page	Sponsor legal address update	To align with current GSK policy
Section 1.1 Synopsis Methodology Part 1B Design Section 4.1.2 Part 1B Design Section 11 APPENDIX 1. REGULATORY, ETHICAL, AND	Language updated to indicate that the dose escalation committee (DEC) will review safety data and will determine the niraparib/dostarlimab dosing strategy	To more clearly describe the role of the DEC in the dose escalation decision-making process overall

Section # and title	Description of change	Brief rationale
STUDY CONSIDERATIONS Committees Structure		
Section 1.1 Synopsis Main Criteria for Inclusion; Section 5.1 Participant Inclusion Criteria Point 03	Addition of relevant time point ("at screening") and of lesion type to be assessed	To clearly indicate at what point in the study disease characteristics were to be evaluated and to describe exactly what type of lesions were to be tracked
Section 1.1 Synopsis Main Criteria for Exclusion; Section 5.2 Participant Exclusion Criteria Point 15	Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic anticancer therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study .	To revert the wording to that in Protocol Amendment 04, which provided more specific criteria for enrollment of participants with ongoing toxicities.
Section 1.3 Schedule of Activities (SoA) Footnote x	"Cycle 1 Day 1 2.5 hour samples must be collected at the scheduled time ±0.5 hour" was added	To more specifically define the permitted sample collection window
Section 1.3 Table 3 Schedule of Activities Table 4 Tumor Assessment Flowchart	Addition of text indicating bone marrow evaluation is required for all participants to confirm response.	To clarify timing of required bone marrow assessments during response evaluation
Section 4.7.2.2 Dostarlimab	Addition of extensive text on recognition and management of immune-mediated AE related to dostarlimab	To update and further clarify information around toxicities associated with dostarlimab treatment
Section 4.7.2.2. Dostarlimab and Table 10 Renal failure or nephritis	Addition of treatment recommendation for Grade 3-4 renal failure or nephritis	To provide additional guidance for specific immune-mediated toxicity management
CCI		
Section 6.8.2 Prohibited Medications	Text was updated with new information particularly with respect to drug-drug interactions	To provide up-to-date information to investigators for use of niraparib by participants taking concomitant therapies

Section # and title	Description of change	Brief rationale
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Guidance for recording and reporting SAE information after participant is no longer in the study was added	To provide more comprehensive directions for SAE reporting
Section 8.4.1 PK Sample Collection	Text about analysis of collected PK samples was added	To provide clarity on conditions under which PK sample analysis may proceed
Section 11 APPENDIX 1. REGULATORY, ETHICAL, AND STUDY CONSIDERATIONS Committee Structure Early Safety Data Review AND/OR Committee	The text "Part 2 Safety Run-in" was added	To clarify that the Dose Escalation Committee would review and consider data from both Part 1 and Part 2 Safety Run-in.
Section 11 APPENDIX 1. REGULATORY, ETHICAL, AND STUDY CONSIDERATIONS Source Documents	Examples were added of contracted third parties and of possible source data that could be shared with these third parties	To provide further clarification about the types of individuals who potentially might have access to and review source data and the types of source data that might be reviewed
Section 11 APPENDIX 4 GUIDELINES FOR ASSESSMENT OF DISEASE, DISEASE PROGRESSION AND RESPONSE CRITERIA – ADAPTED FROM RECIST 1.1	Text about non-measurable disease was removed as well as text about no target lesions at baseline and Table 19	To align text with the protocol requirements that participants must have measurable/evaluable disease at baseline to be eligible.
Section 11 APPENDIX 4 GUIDELINES FOR ASSESSMENT OF DISEASE, DISEASE PROGRESSION AND RESPONSE CRITERIA – ADAPTED FROM RECIST 1.1	Text about confirmation criteria were updated	To clarify the need for confirmation of PR or CR and to direct reader to Table 4 for additional guidance.
Section 11 APPENDIX 5 GUIDELINES FOR ASSESSMENT OF DISEASE, DISEASE PROGRESSION AND RESPONSE CRITERIA IN PARTICIPANTS WITH NEUROBLASTOMA – ADAPTED FROM REVISED INTERNATIONAL NEUROBLASTOMA RESPONSE CRITERIA (INRC)	Text about confirmation of responses was added	To provide guidance on timing of confirmatory scans and to direct reader to Table 4 for additional instructions.
Section 11 APPENDIX 8 LIVER SAFETY: REQUIRED ACTIONS, MONITORING, AND FOLLOW-UP TO ASSESS CAUSALITY OF LIVER EVENT	Text for follow-up needed to assess causality was updated to read: Blood and serum sample for PK analysis of niraparib and dostarlimab, respectively,	To clarify steps required for acceptable follow-up of liver toxicity/event

Section # and title	Description of change	Brief rationale
	obtained within 144 hours after last dose of study intervention[5]	
Throughout document	Minor corrections and formatting adjustments were made	To add clarification and increase readability

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: GlaxoSmithKline	
Name of Investigational Product: Niraparib, dostarlimab	
Name of Active Ingredient: Niraparib, dostarlimab	
Title of Study: A Phase 1, Multicentre, Open-label, Dose escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients with Recurrent or Refractory Solid Tumours	
Study Centre(s): Multicentre	
CCI [redacted]	**Phase of development:** Phase 1

Objectives:

The following are the objectives for Part 1 of this study. The objectives for Part 2 of this study will be presented in each cohort-specific supplement, as applicable.

Primary:

The primary objectives for Part 1 of this study are as follows:

- Part 1A: to establish the recommended Phase 2 dose (RP2D) of the combination of niraparib tablet and dostarlimab in paediatric participants
- Part 1B: to establish the RP2D of the combination CCI [redacted] in paediatric participants

Secondary:

The secondary objectives for Part 1 of this study are as follows:

- to evaluate additional measures of anticancer activity (including objective response rate [ORR] and duration of response [DOR]) in paediatric participants
- to evaluate the safety and tolerability of the combination of CCI [redacted] in paediatric participants
- to characterise the pharmacokinetics (PK) of the combination of niraparib and dostarlimab in paediatric participants
- to assess the immunogenicity of dostarlimab in paediatric participants
- CCI [redacted]

Scope of Master Protocol:

This is a master protocol (213406) consisting of the core protocol and the study design for Part 1. The study design and endpoints for Part 2 of this study are outlined in separate cohort-specific supplements; namely:

- Safety Run-in: Cohort of both osteosarcoma and neuroblastoma participants to assess the safety and tolerability of the CCI [redacted] by assessing dose limiting toxicity (DLT) events and Grade ≥3 thrombocytopenia adverse events (AEs).
- Supplement A: Expansion Cohort of participants with osteosarcoma to assess the antitumour activity of the combination of niraparib and dostarlimab, as determined primarily by the progression-free survival rate at 6 months using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.
- Supplement B: Expansion Cohort of participants with neuroblastoma to assess the antitumour activity of the combination of niraparib and dostarlimab, as determined primarily by ORR using International Neuroblastoma Response Criteria (INRC).

Methodology:

This is a Phase 1, multicentre, open-label, dose escalation study (Part 1) with a Safety Run-in and Cohort Expansion component (Part 2) (see Figure 1). The study will consist of an initial dose escalation portion conducted in participants with CCI [redacted] Part 1A, a dose escalation to determine the RP2D of the combination of CCI [redacted], included participants who were able to swallow the CCI [redacted] and who had a body weight of ≥20 kg. Part 1B, a dose escalation to determine the RP2D of the combination of CCI [redacted], under Protocol Amendment 03 (or earlier), included participants who could not swallow CCI [redacted] or who had a body weight of <20 kg. Part 1B under Protocol Amendment 05 will include participants who are <8 years of age and will receive a modified CCI [redacted]. In Part 2 of the study under Protocol Amendment 03, the RP2D regimen established in Part 1A of the study was evaluated for efficacy and safety in disease-specific expansion cohorts. Part 2 under Protocol Amendment 05 will include participants who are ≥8 years old. In Part 2, a Safety Run-in evaluating a CCI [redacted] will be conducted prior to potential further enrolment into disease-specific expansion cohorts, as outlined in the specific supplements.

Part 1 Dose Escalation Design

CCI [redacted]

CCI [redacted]

Part 1A Design

CCI [redacted]

Participants in Cohort 0 were dosed in a staggered fashion. At this dose level, no more than 3 participants were allowed to receive an initial dose of study treatment until the first 3 participants had all completed at least 1 cycle of study treatment and the resulting data from all 3 participants had been reviewed. This was to ensure an adequate interval for observation and assessment of potential acute AE. Although not needed, dosing strategy for subsequent participants after the initial 3 participants dosed was to have been made by the Dose Escalation Committee (DEC) if >1 DLT was observed in the first 3 participants within the first cycle of treatment (see Appendix 1 for details regarding the DEC).

If Cohort 0 CCI [redacted] was deemed safe based on the mTPI-2 parameters described above, 2 cohorts were to have opened: Cohort 1A and Cohort 1B. If both Cohorts 1A and 1B were considered safe, then Cohort 2 CCI [redacted] was to be opened. If the Cohort 2 dose level was deemed safe, this ***may have been*** considered the RP2D for the niraparib tablet formulation. If the dose level from Cohort 2 was not cleared for use, the RP2D was to be the dose level from Cohort 1B. If only 1 cohort of Cohorts 1A and 1B was deemed safe, then that dose level was to be considered the RP2D. Lastly, if neither Cohort 1A nor 1B was deemed safe, the combination dose level from Cohort 0 was to be the RP2D.

Part 1A Cohort 0, Cohort 1A, and Cohort 1B were evaluated. Cohort 1B was not cleared; therefore, no participants were enrolled into Cohort 2. Further details regarding cohorts and RP2D determination are outlined in Section 4 of the protocol.

The original RP2D of niraparib and dostarlimab was established for the niraparib tablet formulation in Part 1A. Part 2 (disease-specific expansion cohorts, as described in cohort-

specific supplements to this protocol) was opened to accrual for a limited number of participants who were able to swallow the CCI [redacted]. In addition, Part 1B was opened once the RP2D was established in Part 1A and the niraparib TfOS was available.

See Figure 2 for a schema of the Part1A study design.

Part 1B Design

Previously, under Protocol Amendment 03 (or earlier), in Part 1B CCI [redacted]

Originally under Protocol Amendment 03, 3 participants were dosed in Part 1B Cohort 1; however, enrolment in Part 1B Cohort 1 was paused to investigate incidences of Grade 3 and Grade 4 thrombocytopenia observed in participants in Part 1B and in the Part 2 Neuroblastoma Cohort Expansion, and the original Part 1B portion of the study did not advance past Cohort 1. Following review and analysis of clinical, safety, and PK data for all study participants, CCI [redacted] described in Section 2.6.3.1 and Table 7.

Under Protocol Amendment 05, in Part 1B CCI [redacted] the starting dose level for dostarlimab (DL1) will be the RP2D as determined from Part 1A CCI [redacted], and the starting dose level for niraparib is outlined in Section 2.6.3.1of the protocol (and Section 4.1.2 and Figure 5).

Under Protocol Amendments 04 and 05, the study design for Part 1B has been updated as shown in Figure 5. PK evaluations will be performed in at least 6 participants in each cohort unless enrolment into the cohort is closed prematurely due to toxicity.

Enrolment into each Part 1B cohort will take participant age into consideration, with the intent to distribute enrolment across 3 age categories: 6 months to <2 years; ≥2 years to <6 years; and ≥6 years to <8 years. Enrolment into each cohort will be limited to no more than 4 participants aged 6 years or older out of the first 6 participants. The remaining 2 participants out of the first 6 participants in each cohort must be younger than 6 years.

Once enrolment into Cohort A has reached the target 6 participants (or 8, if necessary), safety and PK data will be evaluated and the DEC will decide to open either Cohort B or Cohort C or to declare the Cohort A dose to be the RP2D. Decision steps are described below.

If Cohort B is to be opened, but at least 1 participant from the youngest age category (6 months to <2 years) has not been enrolled in Cohort A, the first potential participant aged 6 months to <2 years to join the study will be enrolled into Cohort A to permit safety evaluation of the starting niraparib and dostarlimab dose levels. Data from this ≥6 months to <2 years of age participant will not contribute to the decision for the next dose level, but may be used to evaluate safety and PK within the age category.

The DEC will review all relevant safety and PK data immediately after all participants treated in the same dose cohort have passed the DLT period and determine the dosing strategy for subsequent participants.

Cohort A

Participants in Cohort A will be dosed in a staggered fashion, meaning no more than 2 participants will be allowed to receive the initial dose of study treatment until each participant has completed 2 cycles of study treatment and the clinical safety data from both participants have been reviewed. This is to ensure an adequate interval for observation and assessment of tolerability of the dose.

- If DLTs or Grade ≥3 thrombocytopenia are observed in ≤1 of the first 2 dosed participants and it is deemed safe to proceed by the study team, a third participant will be allowed to receive the initial dose of study treatment. No additional participants will be allowed to receive study treatment until the third participant has completed at least 2 cycles of study treatment and the resulting data have been reviewed by the study team.
- If DLTs or Grade ≥3 thrombocytopenia are observed in <2 of the first 3 dosed participants, Cohort A will continue to enrol up to 6 evaluable participants. If a DLT is observed in 2 of the first 6 dosed participants, Cohort A will be expanded to 8 DLT-evaluable participants.
- If DLTs or Grade ≥3 thrombocytopenia are observed in both of the first 2 dosed participants, Part 1B will be paused. Safety data for the first 2 dosed participants will be reviewed by the DEC. The dosing strategy for subsequent participants will be determined by the DEC. (See Appendix 1 for details regarding the DEC.)
- If DLTs or Grade ≥3 thrombocytopenia are observed in 2 of the first 3 dosed participants, Part 1B will be paused and safety data and PK data will be reviewed by the DEC. The dosing strategy for subsequent participants will be determined by the DEC.
- If 8 participants have been enrolled and if DLTs are observed in 3 or more of 8 DLT-evaluable participants, the dose level will not be cleared and the decision about the next dose level will be made by the DEC (i.e., to proceed to Cohort C with niraparib dose level -1 [DL-1]).

If Cohort A is deemed safe based on the mTPI-2 parameters, results of the niraparib PK assessment will be taken into consideration when determining the RP2D. If the PK exposure for the niraparib TfOS is consistent with the exposure observed in adults, the niraparib dose in Cohort A will be the basis of determining the RP2D for the TfOS.

If the PK exposure for dostarlimab in Cohort A is consistent with the exposures observed in adults, then the dose level of niraparib and of dostarlimab from Cohort A will be determined to be the RP2D.

If the PK exposures observed in Cohort A with the niraparib TfOS are substantially lower than those observed in adults, a dose escalation cohort (Cohort B) will be opened.

Cohort B

The dose of niraparib for Cohort B will be determined based on the PK evaluation in Cohort A, and the dose level of dostarlimab will remain the same as in Cohort A.

If Cohort B is deemed safe based on the mTPI-2 parameters, results of the niraparib PK assessment in Cohort B will be taken into consideration when determining the RP2D for TfOS.

If the PK exposure for the niraparib TfOS in Cohort B is consistent with the exposures observed in adults, the niraparib dose in Cohort B will be the basis of determining the RP2D for the TfOS.

Cohort C

If Cohort A is not cleared based on the mTPI-2 parameters described above, Cohort C will be opened using a reduced niraparib dose, determined based on the niraparib PK evaluation in Cohort A. The dose of dostarlimab will be the same as in Cohort A.

If Cohort C is deemed safe based on the mTPI-2 parameters described above, results of the niraparib PK assessment in Cohort C will be taken into consideration when determining the RP2D for TfOS.

If the PK exposure for niraparib TfOS in Cohort C is consistent with the exposures observed in adults, the niraparib dose level in Cohort C will be the basis of determining the RP2D for niraparib TfOS.

Cohort D

If the exposures of dostarlimab observed in Cohorts A and B (or Cohorts A and C) are substantially lower than those observed in adults, a dose escalation cohort (Cohort D) will be opened. The dose of dostarlimab for Cohort D will be determined based on the dostarlimab PK evaluation in Cohorts A and B (or Cohorts A and C). A CCI [redacted] may be tested. The dose level of niraparib in Cohort D will be the niraparib RP2D as determined from evaluation in Cohorts A, B, and/or C.

If Cohort D is deemed safe based on the mTPI-2 parameters described above, the dose level of dostarlimab from Cohort D will be the RP2D in combination with the niraparib RP2D. If Cohort D is not cleared, then the dose level of dostarlimab from Cohort A CCI [redacted] will be the RP2D in combination with the niraparib RP2D.

If Cohort C is not deemed safe, the study will not continue as designed.

Alternate niraparib schedules may be implemented for niraparib, if appropriate.

Additional dose levels of niraparib and/or dostarlimab may be evaluated based on safety and PK data from the specific cohorts. Any niraparib dose level other than DL1, DL2, or DL -1 must first be evaluated in combination with dostarlimab DL1 CCI [redacted] prior to evaluating with dostarlimab at DL2 or higher.

Once the RP2D for the combination of the CCI [redacted] is determined in Part 1B of the study, participants <8 years of age will be eligible for enrolment into the Part 2 disease-specific expansion cohorts (described in cohort-specific supplements to this protocol).

In addition, once the RP2D is determined, the RP2D cohort in Part 1B will remain open until completion of Part 2 overall for additional enrolment to reach a minimum of N=3 participants enrolled in Part 1B RP2D within each age category: ≥6 months to <2 years; ≥2 year to <6 years; and ≥6 years to <8 years.

Dose Limiting Toxicity

The DLT observation period is 42 days following the initiation of study treatments (i.e., approximately the first 2 treatment cycles). A participant will be considered unevaluable for DLT assessment if, for reasons other than DLT, the participant does not complete the DLT observation period or receives <80% of the intended niraparib dose (e.g., missed 9 or more doses; reason for missed doses may include, but is not limited to, noncompliance) or <2 infusions of dostarlimab. Participants considered unevaluable may be replaced after consultation between the Sponsor and Investigator. A participant may continue on study treatment following a DLT if the Investigator determines doing so is in the best interest of the participant, after discussion by the Investigator with the GSK Medical Monitor, and after appropriate recovery from the DLT by the participant.

DLT is defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related Grade 4 nonhaematologic clinical (nonlaboratory) AE
- any treatment-related Grade 3 nonhaematologic clinical (nonlaboratory) AE not resolving to Grade ≤1 within 48 hours of initiating optimal medical intervention
- any treatment-related Grade 3 or 4 nonhaematologic laboratory abnormality if any of the following also occur:
  - the abnormality leads to hospitalisation
  - the abnormality persists for ≥7 days from the time of AE onset and participant is symptomatic from the AE and/or requires intervention
- any treatment-related haematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for ≥7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding or requiring platelet transfusion
  - Grade 4 neutropenia persists for ≥7 days, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥72 hours
  - Grade 4 anaemia or Grade 3 anaemia requiring blood transfusion
- any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2
- any treatment-related toxicity resulting in the participant receiving <80% of the intended niraparib dose and/or <2 dostarlimab infusions due to dose modification/interruption/reduction
- any treatment-related Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks
- any treatment-related Grade ≥2 immune-related endocrine toxicity that requires hormone replacement, except Grade 2 thyroiditis or thyroid dysfunction
- any treatment-related Grade 2 colitis or diarrhoea that persists for ≥7 days without resolution to Grade ≤1 despite adequate steroid therapy
- any Grade 3 or 4 immune-related AE that does not resolve to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy

- Grade 3 or higher infusion-related reaction
- any grade of hemophagocytic lymphohistiocytosis
- any grade of Posterior Reversible Encephalopathy Syndrome (PRES)
- any treatment-related Grade 5 AE

Safety monitoring in Part 2 is described in the cohort-specific supplements.

General Study Conduct

This study consists of a Screening Period (Day -28 to Day -1), a Treatment Period, an End of Treatment (EOT) Visit, a Safety Follow-up Visit, and a Follow-up Assessment Period. During the Treatment Period, study treatment administration will occur in 3-week cycles. Participants will receive niraparib daily or on an alternative schedule in combination with dostarlimab Q3W until progressive disease (PD), unacceptable toxicity, withdrawal of consent, Investigator's decision, or death.

Participants must have a baseline tumour assessment (computed tomography [CT] or magnetic resonance imaging [MRI]) of the chest, abdomen, pelvis, and any additional sites as clinically indicated within 28 days prior to the first dose of study treatment. Participants with neuroblastoma must also have a baseline tumour assessment via metaiodobenzylguanidine-single-photon emission computed tomography/computed tomography (MIBG-SPECT/CT) or fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-positron emission tomography [PET]/CT) within 42 days prior to the first dose of study treatment. A baseline brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT) is required for participants with previously treated brain metastases. (Participants with previously treated brain metastases may participate under the conditions detailed in exclusion criterion 5 in this master protocol and in the exclusion criteria of each cohort-specific supplement for Part 2.)

Tumour assessments by CT or MRI of sites involved by disease at baseline and of any additional sites as clinically indicated will be done postbaseline, as will MIBG-SPECT/CT or FDG-PET/CT tumour assessments (participants with neuroblastoma only). Tumour assessments should be conducted every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation of participant from overall study participation (e.g., death, participant's request, loss to follow-up), whichever comes first. Tumour assessments should be scheduled using the date of the first dose of study treatment as the reference date for all time points and are not to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to study treatment delay is not permitted.

Bone scan, whole body MRI, or PET scan will be carried out at baseline for all participants in Part 1 (excluding participants with neuroblastoma) and in the Part 2 Osteosarcoma Expansion Cohort within 84 days prior to the first dose of study treatment in order to detect bony sites of disease. Subsequent assessments are to be performed during the Treatment Period when clinically indicated. If the baseline bone scan, whole body MRI, or PET scan is positive for

metastatic bone disease, a repeat assessment is required for confirmation of partial response (PR) or complete response (CR) or if clinically indicated.

The same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant.

Clinical assessment of superficial lesions should be carried out on the same date as the imaging studies or no later than 3 days thereafter and must be recorded in the participant's electronic case report form (eCRF).

Participants with neuroblastoma will undergo bone marrow assessments at Screening and, if positive at baseline, every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation of participant from overall study participation (e.g., death, participant's request, loss to follow-up), whichever comes first.

Participants who have a PR or CR while on treatment and who discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.

Blood samples to assess niraparib PK, dostarlimab PK, and dostarlimab antidrug antibodies (ADAs) and neutralising antibodies (NAb) will be collected from all participants pre- and postdose at the time points specified in Table 3. CCI [redacted] Blood samples should be collected in order of priority as outlined in Section 8.2. Tumour samples will be collected from all participants in Part 2 and also from Part 1 participants, but only under specific circumstances such as a treatment response.

Safety assessments conducted throughout the Treatment Period include symptom-directed physical examinations, electrocardiograms (ECGs), vital signs, and clinical laboratory assessments, including complete blood count (CBC) with differential, coagulation profile, chemistry, thyroid function panel, and pregnancy testing (irrespective of prior medical treatment). Psychological assessments will be administered as per local standard of care.

CCI [redacted]

All participants will undergo an EOT Visit conducted within 7 days of the decision to discontinue study treatment and a Safety Follow-up Visit 30 (+7) days after the last date of study treatment administration. Participants are expected to complete the Safety Follow-up Visit regardless of reason for study treatment discontinuation and even if they have started alternative anticancer therapy. During the long-term Follow-up Assessment Period, participants will be followed via clinic visit or telephone contact (if an in-person visit is not possible) every 90 (±14) days after last dose of study treatment for the first year, every 180 (±14) days for the subsequent 2 years, and yearly (±14 days) for an additional 2 years (5 years total), or until the start of alternative anticancer therapy (unless there is an ongoing AE/serious

AE [SAE] that must be followed until resolved, stabilised, or otherwise explained), or until the participant withdraws from the study overall, is lost to follow-up, or dies (whichever occurs earlier).

Collection and recording of all AEs for each participant will start on the day of informed consent/assent. Nonserious AEs will be collected until 30 days after the last dose of study treatment. SAEs will be collected until 90 days after the last dose of study treatment (or to a minimum of 30 days after the last dose of study treatment if the participant starts alternative anticancer treatment). However, any SAEs assessed as related to study participation or related to study treatment will be collected through the Follow-up Assessment Period. Adverse events of special interest (AESIs) are defined in Appendix 2; AESIs will be collected through the Follow-up Assessment Period as described in Section 8.3.6. Details of all pregnancies in female participants and, if indicated, female partners of male participants who receive study treatment will be collected until 180 days after the last dose of study treatment in female participants and 90 days after the last dose of study treatment for female partners of male participants. In addition, all ongoing AEs and SAEs are to be followed, regardless of start of alternative anticancer therapy, until the event is resolved, stabilised, or otherwise explained or until the participant has withdrawn consent to the study overall, is lost to follow-up (as defined in Section 7.4), or has died.

Number of Participants (actual and planned): Under Protocol Amendment 03, approximately 56 participants were planned to be enrolled in Part 1 of the study, including approximately 32 participants in Part 1A and approximately 24 participants in Part 1B (unless the incidence of DLTs dictated fewer participants as per the Dose Escalation Plan described in Section 4.1).

A total of 23 participants were enrolled into Part 1A Cohorts 0, 1A, and 1B. Part 1A Cohort 1B was not deemed to be safe, and, as a result, no participants were enrolled into Part 1A Cohort 2. In addition, a total of 3 participants were enrolled into Part 1B Cohort 1, for which enrolment into Part 1B Cohort 1 was prematurely stopped due to DLTs of Grade ≥3 thrombocytopenia.

Under Protocol Amendment 05, it is anticipated that 1 to 3 cohorts (8 participants per cohort or approximately 24 participants overall) may be enrolled in Part 1B, unless the incidence of DLTs dictates fewer participants as noted above for Part 1A and in Section 4.1. Additional cohorts (including up to 8 participants per cohort) may be opened in Part 1B if needed to evaluate alternative niraparib dose levels. Lastly, up to 5 additional participants may be enrolled into Part 1B to further evaluate the youngest participant group(s) if not represented.

Numbers of participants for the Part 2 Osteosarcoma and Neuroblastoma Expansion Cohorts are discussed in the relevant protocol supplement.

Diagnosis and Main Criteria for Inclusion:

Participant will be eligible for Part 1 of the study if all of the following criteria are met:

1. CCI [redacted]

CCI [redacted]

2. Participant is child or adolescent ≥6 months to <18 years old at the time of informed consent/assent. If a participant is enrolled under Protocol Amendment 05, the participant must be ≥6 months to <8 years old at the time of informed consent/assent.
3. Participant with disease other than neuroblastoma has radiologically measurable disease at screening that can be tracked as RECIST v1.1 target lesion(s).

   Participant with neuroblastoma has measurable/evaluable target and/or non-target disease by INRC at screening. Neuroblastoma participants with recurrent/relapsed bone metastasis that is metaiodobenzylguanidine (MIBG)-positive (or FDG-positive, for MIBG-nonavid tumours) as only site of disease are eligible.
4. Under Protocol Amendment 03 (or earlier), a participant in Part 1A must be able to swallow the CCI [redacted] and have a baseline body weight of ≥20 kg. Participants in Part 1A who are unable to swallow the CCI [redacted] or who have a baseline body weight <20 kg are eligible to receive the niraparib CCI [redacted] only. As of Protocol Amendment 04, there are no inclusion criteria addressing ability to swallow niraparib tablets.
5. Performance status must be ≥60% on the Karnofsky scale for participants >16 years of age and ≥60% on the Lansky scale for participants ≤16 years of age.

   Note: Neurologic deficits in participants with brain metastases must have been stable for at least 7 days prior to study enrolment. Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status.
6. Participant has adequate organ function, defined as follows:

   Note: The participant must not have received blood transfusion, growth factors, or platelet stimulating agents in the 14 days prior to providing a sample for haematologic analysis nor erythropoietin in the prior 6 weeks.

   a. absolute neutrophil count (ANC) ≥1000/µL
   b. platelets ≥100 000/µL
   c. haemoglobin ≥8 g/dL or ≥5.0 mmol/L

d. serum creatinine≤1.5×upper limit of normal (ULN) for age or calculated creatinine clearance or radioisotope glomerular filtration rate ≥60 mL/min/1.73m^2
e. total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 × ULN
f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case AST and ALT must be ≤5 × ULN
g. international normalised ratio or prothrombin time (PT) ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
h. activated PTT ≤1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   a. Is not a woman of childbearing potential (WOCBP).

   Or

   b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3, from the Screening Visit through at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
   c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours prior to the first dose of study treatment and irrespective of prior medical treatment.

   Additional requirements for pregnancy testing during and after the Treatment Period are located in Section 8.2.9.

   The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. A male participant of reproductive potential is eligible to participate if he agrees to the following starting with the first dose of study treatment through at least 90 days (a spermatogenesis cycle) after the last dose of study treatment:

   a. refrain from donating sperm

      plus, either:

   b. be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

      or

   c. must agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.

9. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.

Inclusion criteria for Part 2 of the study are described in each cohort-specific supplement.

Main Criteria for Exclusion:

Participant will not be eligible for study entry if any of the following criteria are met:

1. Participation presents unacceptable risk to the prospective participant based on the Investigator's judgment.
2. Participant has known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.
3. Participant has a known history of myelodysplastic syndrome or acute myeloid leukaemia.
4. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying antirheumatic drugs, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
5. Participant has known active CNS metastases, carcinomatous meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are clinically stable and have no evidence of new, enlarging, or progressing brain metastases (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks (28 days) prior to the first dose of study treatment. In addition, the participant must not have been using steroids for at least 7 days prior to the first dose of study treatment. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.
6. Participant had a known additional (second primary) malignancy that progressed or required active treatment within the last 2 years.
7. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining assent/consent).
8. Participant has a condition (such as transfusion-dependent anaemia or thrombocytopenia), requirement for therapy, or laboratory abnormality that might confound the study results or interfere with the participant's participation for the full duration of the study treatment.
9. Participant is pregnant, breastfeeding, or expecting to conceive within the projected duration of the study, starting with the Screening Visit through 180 days after the last dose of study treatment.

   No data are available regarding the presence of dostarlimab or niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from dostarlimab and/or niraparib, female participants should not breastfeed during treatment with dostarlimab and/or niraparib and for at least 4 months after the last dose of dostarlimab or at least 30 days after the last dose of niraparib, whichever is longer.

10. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
11. Participant has a known history of HIV (type 1 or 2 antibodies).
12. Participant has documented presence of HbsAg and/or HBcAb at Screening or within 3 months prior to first dose of study intervention. Participants with a negative HbsAg and positive HbcAb result are eligible only if HBV DNA is negative (Appendix 12)
13. Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.
14. Participant has had any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer treatment and that persisted >4 weeks (28 days).
15. Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic anticancer therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.
16. Participant had toxicity related to prior immunotherapy that led to treatment discontinuation.
17. Participant had treatment with systemic anticancer therapy (investigational agent or device, or approved chemotherapy, targeted therapy, immunotherapy, or other systemic therapy) within 3 weeks or 5 half-lives, whichever is shorter, prior to the first dose of study treatment; radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment; or any radiation therapy within 1 week prior to the first dose of study treatment.
18. Participant has not recovered adequately from AEs or complications from any major surgery prior to starting study treatment.
19. Participant has received a live vaccine within 30 days of planned start of study treatment.
20. Participant has clinically significant cardiovascular disease (e.g., significant cardiac conduction abnormalities, uncontrolled hypertension, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, and history of cerebrovascular accident) within 6 months of enrolment.
21. Participant has heart rate-corrected QT interval prolongation at screening >450 msec or >480 msec for participants with bundle branch block.

    Notes:

    - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine read or manually over read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual participant must be determined prior to initiation of the study and used consistently for eligibility and study assessments.

22. Participant has received a solid organ transplant.
23. Participant has a documented presence of HCV antibody at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, if a confirmatory HCV RNA test is negative and the participant otherwise meets entry criteria.
24. Participant has a documented presence of HCV RNA at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well.

Exclusion criteria for Part 2 of the study are described in each cohort-specific supplement.

Investigational Product, Dosage and Mode of Administration:

CCI [redacted]

CCI [redacted] Dostarlimab infusion will be administered before the niraparib dose at the study site on Day 1 of each 21-day treatment cycle (Q3W). Dostarlimab will be administered through a 30-minute infusion. A window between -5 minutes and +15 minutes is permitted, in the absence of any clinically significant infusion-related reaction that would necessitate interruption and/or increased infusion interval.

Duration of Treatment: Study treatment may continue until documented PD, unacceptable toxicity, withdrawal of consent, Investigator's decision, or death.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety

- DLTs during the first 42 days following the initiation of study treatment (i.e., approximately the first 2 treatment cycles) in Part 1.
- The incidence of treatment-emergent adverse events (TEAEs) occurring while participants are on treatment until 30 days after the last dose of study treatment for AEs, until 90 days after the last dose of study treatment for SAEs (or 30 days after last dose for SAEs if the participant starts alternative anticancer treatment), and study treatment-related SAEs and AESIs will be collected through the Follow-up Assessment Period (see Section 8.3.6) until the discontinuation of the participant from overall study participation.
- Changes in clinical laboratory parameters (haematology, chemistry, thyroid function), urinalysis (if obtained), vital signs, physical examinations, ECGs, and usage of concomitant medications.

Efficacy

- ORR, defined as the proportion of participants with a best overall response (BOR) of confirmed CR or PR as determined by the Investigator using RECIST v1.1 or INRC (for participants with neuroblastoma only).
- DOR, defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 or INRC (for participants with neuroblastoma only) based on Investigator assessment, or death (whichever occurs first).

Pharmacokinetics

The PK parameters will be estimated by population PK methods with appropriate adjustment for key covariates including age and body weight.

CCI [redacted]

Antidrug Antibodies

Dostarlimab ADAs will be analysed in a tiered approach (i.e., screening, confirmation, titre, and neutralising antibody assay) using electrochemiluminescence, if appropriate.

Statistical Methods:

Sample Size Consideration

The sample size of approximately 56 participants in total is not based on formal statistical hypotheses but is estimated based on an mTPI-2 dose escalation design for Part 1 including approximately 7 cohorts (4 cohorts originally planned in Part 1A under Protocol Amendment 03 and 3 cohorts planned in Part 1B under Protocol Amendments 04 and 05 [8 participants per each of the 7 cohorts]). Up to 5 additional participants may be enrolled to further evaluate the youngest participant group(s) if not represented.

Analysis Populations

- The DLT-evaluable Population consists of participants in Part 1 who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT.
- The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
- The Intent-to-Treat (ITT) Population includes all participants who receive any study medication and have measurable baseline tumour assessment and/or, for neuroblastoma participants, MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid tumours) at baseline.
- The modified ITT (mITT) Population includes all participants who receive any study medication, have measurable baseline tumour assessment, and/or, for neuroblastoma

participants, MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid-tumours) at baseline, and have at least 1 postbaseline tumour assessment.

- The Per protocol Population includes all participants in the mITT Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.
- The PK Population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK Populations are defined separately for each agent.
- Immunogenicity (ADA) Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

General Methods

All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented.

CCI [redacted]

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan.

Efficacy Analysis

The number and proportion of participants with an objective response will be tabulated by dose cohort and overall. ORR will be calculated along with its estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR will be performed using Kaplan-Meier method, including quartile estimates and two-sided 95% CI.

Safety Analysis

For Part 1, the incidence of DLTs will be summarised by study part and cohort for the DLT-evaluable Population. For all parts of the study, additional safety data will be summarised for the Safety Population.

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) v20.0 or later. All AEs occurring during the study will be included in by-participant data listings and tabulated by MedDRA system organ class and preferred term. Safety parameters will include the incidence of TEAEs, related TEAEs, serious TEAEs, TEAEs of Grade 3 or greater by National Cancer Institute Common Terminology Criteria for Adverse Events v5, TEAEs leading to death, TEAEs leading to treatment discontinuation, and TEAEs leading to

dose modification. AESIs will also be summarised and listed. No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on study will be listed in participant data listings. By-participant listings also will be provided for the following: participant deaths, SAEs, and AEs leading to withdrawal of study treatment.

Clinical laboratory tests, vital signs, ECG results, physical examination findings, performance status, and concomitant medication usage will be listed per participant for each assessment, and descriptive statistics will be tabulated for selected safety parameters.

PK and Immunogenicity Analysis

The PK characteristics of niraparib and dostarlimab will be evaluated in the PK Population using sparse blood sampling and population PK analysis approaches. Serum concentrations of dostarlimab and CCI [redacted] will be presented using descriptive statistics by dose cohort and overall. Summary statistics will include mean, standard deviation, coefficient of variation (CV), geometric mean, geometric mean CV, median, and minimum and maximum values. The CCI [redacted] concentration data may be used to evaluate the age-related metabolism development of niraparib in paediatric participants, if data permit. Niraparib and dostarlimab concentration-time data will be analysed using a population approach. A nonlinear mixed effects model will be used to determine population PK parameters and identify relevant covariates (e.g., age, weight, or disease-related covariates). The data from this study may be combined with data from other studies and the results of these analyses will be described in a separate report.

Serum samples for the determination of anti-dostarlimab antibodies will be aliquots of the same samples collected as for PK. Minimally, ADA will be analysed using electrochemiluminescence with samples collected prior to all dostarlimab doses as indicated in the Schedule of Activities, as well as at EOT, at the Safety Follow-up Visit (30-days post-treatment), and at the first Follow-up Visit (90-days post-treatment). The summary of number and percent of participants who become positive for ADAs and who develop NAb will be based on dose regimen, part, visit/time, and overall.

CCI [redacted]

1.2. Schemas

CCI

CCI

[redacted]

1.3. Schedule of Activities (SoA)

The Schedule of Activities (SoA) for Part 1, inclusive of cohort-specific activities is provided in Table 3. The tumour assessment flowchart is presented in Table 4. The SoAs specific to the cohorts will be provided in the supplements.

The study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. Regulatory, ethical, and study oversight considerations are provided in Appendix 1.

Table 3: Schedule of Activities

Protocol Activity	Screening Period	Treatment Period					EOT Visit[a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment)[c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Informed consent/assent[d]	X								
Demographics and medical history	X								
Performance status	X								
Inclusion/exclusion criteria	X								
CCI									
Physical examination	X	A complete physical examination is to be conducted at Screening and EOT only, and as clinically indicated.							
Psychological assessments[f]	X						X		
Vital signs, weight, and height[g]	X	X	X	X	X	X (Cycle 3 only)	X	X	X

Protocol Activity	Screening Period	Treatment Period					EOT Visit[a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment)[c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
CBC with differential[h]	X	Twice weekly	Twice weekly	Twice weekly	X		X		
Coagulation[h]	X	As clinically indicated					X		
Blood chemistry[h]	X	X	X	X	X		X		
Serum or urine pregnancy test (WOCBP only)[i]	X	X			X		X	X	X
CCI									
12-lead ECG[k]	X				X (Cycle 3 only)		X		
Dostarlimab administration		X			X				
Niraparib dispensed/collected (administered Day 1 after dostarlimab infusion)		X			X		X (Collect-ion only)		

Protocol Activity	**Screening Period**	**Treatment Period**					**EOT Visit**[a,b]	**Safety FUP Visit (30 [+7] Days Post-Treatment)**[b]	**FUP Assessment Period (Every 90 [±14] Days Post-Treatment)**[c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Tumour assessment: CT or MRI [l] – All participants [m]	X[n,o]	Every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first[p]					X[q]		
Tumour assessment: MIBG-SPECT/CT or FDG-PET/CT – Participants with neuroblastoma only [m]	X[n,o]	Every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first[p] Note: MIBG-SPECT/CT should be used for participants with MIBG-avid tumours and FDG-PET/CT should be used as an alternative modality for participants whose tumours do not concentrate MIBG.					X[q]		
Tumour assessment: Bone scan, whole body MRI, or PET scan – Part 1 (excluding participants with neuroblastoma) and Osteosarcoma Expansion Cohort [m, r]	X[o]	Required throughout this interval if clinically indicated and to confirm disease response if baseline scan was positive for metastatic bone disease							

Protocol Activity	Screening Period	Treatment Period					EOT Visit[a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment)[c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Bone marrow assessment – Participants with neuroblastoma only	X[s]	If positive at baseline, every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first. Required for all participants to confirm disease response.					X[q]		
CCI									
AE monitoring [u]	X	X	X	X	X	X	X	X	X
Prior and concomitant medications and nondrug treatments	X	Medications and nondrug treatments will be monitored for study purposes from Screening to at least 30 days following the last dose of study treatment							
Blood sample for dostarlimab PK and/or ADAs and neutralising antibodies [v, w]		X	X (Cycle 1 only)		X (predose, Cycles 4 and 6, and every 6 cycles thereafter)		X	X	X

Protocol Activity	Screening Period	Treatment Period					EOT Visit[a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment)[c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Blood sample for niraparib PK [w, x]		X (Cycle 1 and 2)	X (Cycle 1 only)						
CCI									
Alternative anticancer treatment assessment						X	X	X	X

Abbreviations: ADA=antidrug antibody; AE=adverse event; AESI=adverse event of special interest; ALP=alkaline phosphatase; BP=blood pressure; CCI CBC=complete blood count; CNS=central nervous system; CR=complete response; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; EOT=End of Treatment; FDG-PET/CT=fluorodeoxyglucose-positron emission tomography/computed tomography; FUP=follow-up; G-CSF=granulocyte-colony stimulating factor; HbcAb=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; HCVAb=Hepatitis C virus antibody; INRC=International Neuroblastoma Response Criteria; IV=intravenous; MIBG-SPECT/CT=metaiodobenzylguanidine-single-photon emission computed tomography/computed tomography; MRI=magnetic resonance imaging; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetics; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SAE=serious adverse event; WOCBP=woman of childbearing potential.

a. All participants will undergo an EOT Visit no more than 7 days following the decision to discontinue study treatment for any reason.

b. The Safety FUP Visit and EOT Visit can be combined if both fall within the same window. The Safety FUP Visit is to take place no sooner than 30 days after last dose to permit the protocol-required collection of AEs/SAEs occurring during this 30-day interval. The Safety FUP Visit has a window of +7 days.

c. During the FUP assessment period, participants will be followed via clinic visit or telephone contact every 90 (±14) days after the last dose of study treatment for the first year, every 180 (±14) days for the subsequent 2 years, and yearly (±14 days) for an additional 2 years (5 years total); or until the start of alternative anticancer therapy (unless there is an ongoing AE/SAE that must be followed until resolved, stabilised, or otherwise explained), the participant withdraws from the study overall, is lost to follow-up, or dies (whichever occurs earlier).
d. Informed consent/assent must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day Screening Period.
CCI [redacted]
f. Psychological assessments to be performed as per local standard of care.
g. Vital signs include temperature, blood pressure, heart rate, and respiratory rate. All vital signs will be taken before, every 15 to 30 minutes during, and at the end of every dostarlimab infusion. Throughout the Treatment Period, all vital signs will be monitored at Week 1 of each cycle even if dostarlimab is not administered. In addition, for the first 8 weeks of the Treatment Period (up to and including Cycle 3 Week 2), all vital signs will be monitored at Week 2 and Week 3 of each cycle. Height and weight will be measured at screening, Day 1 of each cycle, EOT, 30-Day Safety Follow-up, and during the FUP Assessment Period.
h. Haematology, coagulation, and chemistry assessments will be performed by local laboratories. Parameters required in this study are listed in Table 15. Haematology, coagulation, and chemistry assessments must be measured within 7 days prior to Cycle 1 Day 1 to confirm eligibility. Haematology and chemistry must be performed and results evaluated prior to study treatment administration. Haematology is to be checked twice each week during the first 2 cycles of study treatment for all participants. Haematology tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the participant's study file, and the results must be entered into the eCRF. If dose interruption or modification is required at any point on study because of haematologic toxicity, weekly blood draws for CBC will be done according to Table 10. Additional haematology or chemistry assessments may be performed according to local standard of care or as clinically indicated. If Cycle 1 Day 1 is no more than 7 days after sample collection for Screening, these samples do not need to be collected again for Cycle 1 Day 1, unless clinically warranted. Additional monitoring for haematology is to be performed after a niraparib dose increase due to a birthday or due to a weight increase that moves participants to a higher CCI [redacted], respectively. Haematology is to be checked twice each week during the first 2 cycles of study treatment after the niraparib dose increase. Blood samples should be collected in order of priority as outlined in Section 8.2.
i. If the participant is a WOCBP, urine or serum pregnancy test will be performed by the local laboratory at the Screening Visit, within 24 hours prior to the first dose of study treatment, on Day 1 of every cycle for the duration of the Treatment Period, at the EOT Visit, at the 30-Day Safety Follow-up Visit, and 180 (±14) days after the last dose of study treatment. Pregnancy testing should occur irrespective of prior medical treatment. The results from these tests must be available and negative before study treatment is administered. Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected.
CCI [redacted]
k. ECG should be repeated at Cycle 3 Week 1 and EOT, as well as during the Treatment or FUP Periods if clinically indicated.
l. CT scans should be performed with contrast agents unless contraindicated for medical reasons. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such a case, CT will be performed without contrast to evaluate the lung parenchyma. If MRI is used to follow -up bone lesion(s), it must be performed prior to any treatment that may affect bone marrow cellularity (e.g., G-CSF). PET/CT may be used according to RECIST v1.1 or INRC (participants with neuroblastoma only) guidelines with full-dose diagnostic CT and as clinically indicated.

m. The same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant. Clinical assessment of superficial lesions should be carried out on the same date as the imaging studies or no later than 3 days thereafter and must be recorded in the participant's eCRF.
n. Participants must have a baseline tumour assessment (CT or MRI) of the chest, abdomen, pelvis, and any additional sites as clinically indicated within 28 days prior to the first dose of study treatment. Participants with neuroblastoma must also have a baseline tumour assessment via MIBG-SPECT/CT or FDG-PET/CT within 42 days prior to the first dose of study treatment. A baseline brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT scan) is required for participants with previously treated brain metastases. (Participants with previously treated brain metastases may participate under the conditions detailed in Exclusion Criterion 5 in this master protocol and in each cohort-specific supplement for Part 2.)
o. Radiologic assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations, if all of the following conditions are met:
    - the CT or MRI tumour assessments were obtained within 28 days prior to the first dose of study treatment/the MIBG-SPECT/CT or FDG-PET/CT tumour assessments were obtained within 42 days prior to the first dose of study treatment (participants with neuroblastoma only)/the bone scan, whole body MRI, or PET tumour assessments were obtained within 84 days prior to the first dose of study treatment (Part 1 [excluding participants with neuroblastoma] and the Osteosarcoma Expansion Cohort),
    - the assessments were performed using the method requirements outlined in RECIST v1.1 or INRC (participants with neuroblastoma only),
    - the same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant, and
    - appropriate documentation indicating that these radiologic tumour assessments were performed as standard of care is available in the participant's source notes.
p. Tumour assessments by CT or MRI of sites involved by disease at baseline and of any additional sites as clinically indicated will be done postbaseline, as will MIBG-SPECT/CT or FDG-PET/CT tumour assessments (participants with neuroblastoma only) (see Table 4). Tumour assessments, including bone marrow assessments, will be conducted on the schedule shown in Table 3. Tumour assessments should be scheduled using the date of the first dose of study treatment as the reference date for all time points and are not to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to study treatment delay is not permitted.
q. Participants who have already demonstrated documented PD as per RECIST v1.1 or INRC (participants with neuroblastoma only) do not need to have tumour assessments repeated at the EOT Visit or during the Post-Treatment FUP. Participants who do not have documented PD at time of study treatment discontinuation will continue to undergo tumour assessments on their original schedule (i.e., every 9 weeks [every 63 ±7 days] from the start of study treatment for the first 12 months and then every 12 weeks [every 84 ±7 days] thereafter), until documented PD, start of alternative anticancer treatment, or discontinuation from overall study participation [e.g., death, participant's request, or participant is lost to follow-up], whichever comes first). Participants who have a PR or CR while on treatment and discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.
r. Bone scan, whole body MRI, or PET scans will be carried out at baseline for all participants in Part 1 (excluding participants with neuroblastoma) and in the Osteosarcoma Expansion Cohort within 84 days prior to the first dose of study treatment to detect bony sites of disease. Subsequent assessments are to be performed during the Treatment Period when clinically indicated (i.e., participant describes new or worsening bone pain, or other signs or symptoms of new/progressing bone metastases are present). If the baseline bone scan, whole body MRI, or PET scan is positive for metastatic bone disease, a repeat assessment is required for confirmation of PR or CR.
s. Bone marrow assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations if obtained within 28 days prior to the first dose of study treatment.

CCI [redacted]

u. AEs will be collected until 30 days after the last dose of study treatment. SAEs will be collected until 90 days after the last dose of study treatment (or to a minimum of 30 days after the last dose of study treatment if the participant starts alternative anticancer treatment). However, any SAEs assessed as related to study participation or related to study

treatment will be recorded through the FUP Assessment Period. AESIs must be recorded on the eCRF. AESI collection periods are described in Section 8.3.6. Any pregnancies that occur in female participants within 180 days after the last dose of study treatment or in partners of male participants within 90 days after the last dose of study treatment are to be reported as described in Section 8.3.5. Pregnancies occurring more than 180 days after last dose of study treatment with an associated SAE (considered causally related to the study treatment by the Investigator) will follow the SAE reporting requirements. All AEs and SAEs will be followed, regardless of start of alternative anticancer therapy, until the event is resolved, stabilised, or otherwise explained; or until the participant has withdrawn consent to the study overall, is lost to follow-up (as defined in Section 7.4), or has died.

v. Blood samples (single sample for all analytes) for serum dostarlimab PK and/or ADA and neutralising antibodies (NAb) will be collected from participants during Cycle 1 at the following time points relative to the start of the dostarlimab infusion: Cycle 1 Day 1 at Predose (PK, ADA, and NAb) and 1 ± 0.5 hours postdose (PK only), Cycle 1 Day 8 at 168 ± 12 hours postdose (PK, ADA, and NAb), and predose on Cycle 2 Day 1 (predose sample must be collected within 12 hours prior to infusion) (PK, ADA, and NAb). Blood samples for serum dostarlimab PK, ADA, and NAb will also be collected at the following time periods: predose in Cycles 4 and 6, every 6 cycles thereafter up to 2 years, and the EOT Visit. In addition, blood samples for serum dostarlimab ADA and NAb will be collected at the Safety Follow-up Visit (30 days post-treatment) and at the first Follow-up Visit (90 days post-treatment). PK, ADA, and NAb samples will be drawn at the same time points and in the same collection, except as noted.
w. The maximum blood volume for each sample for PK, ADA and NAb and exploratory biomarker assessments is 0.8 mL/kg, and the maximum total blood volume allowed for PK, ADA, and NAb, and exploratory biomarker assessments is 1.8 mL/kg per 3-week treatment cycle. Blood samples should be collected in order of priority as outlined in Section 8.2.
x. Blood samples for plasma niraparib and CCI [redacted] (single sample for both analytes) will be collected from participants during Cycle 1 Day 1 at 2.5 and 7 hours after the first dose of niraparib, predose on Cycle 1 Day 8, predose on Cycle 2 Day 1, and Cycle 2 Day 1 at 5 hours after niraparib dose. Additional niraparib PK sampling is to be performed after a niraparib dose increase due to a birthday or after a niraparib dose modification due to a weight increase or decrease. (These additional PK samples will be taken on Day 1 in the first cycle after the dose change at 2.5 and 7 hours postdose, predose on Day 1 of the second cycle after the dose change, and at 5 hours after the niraparib dose on Day 1 of the second cycle after the dose change). Note: Predose samples must be collected within 2 hours prior to dosing; Cycle 1 Day 1 2.5 hour samples must be collected at the scheduled time ±0.5 hour and other samples must be collected at the scheduled time ±2 hours.
y. CCI [redacted]. Blood samples should be collected in order of priority as outlined in Section 8.2.

Table 4: Tumour Assessment Flowchart

Tumour Assessment	Screening Period	Treatment Period	Confirmation of Response[a]	Post-Treatment Follow-Up
CT or MRI of chest, abdomen, pelvis, and any additional sites as clinically indicated	Required	Required, including sites of any other tumour lesions identified at baseline and of any additional sites as clinically indicated	Required, including sites of any other tumour lesions identified at baseline	If PD has been documented: Not required If PD has not been documented: Required, including sites of any other tumour lesions identified at baseline
Brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT)	Required for participants with previously treated brain metastases	Not required unless clinically indicated	Required if baseline scan was positive	Not required unless clinically indicated
MIBG-SPECT/CT for participants with MIBG-avid tumours or FDG-PET/CT as the alternative modality for participants whose tumours do not concentrate MIBG (Participants with neuroblastoma only)	Required	Required	Required	If PD has been documented: Not required If PD has not been documented: Required
Bone scan, whole body MRI, or PET scan (Part 1 [excluding participants with neuroblastoma] and Osteosarcoma Expansion Cohort)	Required	Not required unless clinically indicated	Required if baseline scan was positive for metastatic bone disease	Not required unless clinically indicated

Tumour Assessment	Screening Period	Treatment Period	Confirmation of Response[a]	Post-Treatment Follow-Up
Clinical assessment of superficial lesions	Required	Required for sites of tumour lesions identified at baseline and any additional sites as clinically indicated	Required for sites of tumour lesions identified at baseline	Required for sites of tumour lesions identified at baseline, unless PD has been documented elsewhere
Bone marrow aspirate and biopsy (Participants with neuroblastoma only)	Required	Required for participants with bone marrow involvement at screening	Required for all participants	If PD has been documented: Not required If PD has not been documented: Required for participants with bone marrow involvement at screening

Abbreviations: CT=computed tomography; EOT=End of Treatment; FDG-PET/CT=fluorodeoxyglucose-positron emission tomography/computed tomography; MIBG-SPECT/CT=metaiodobenzylguanidine-single-photon emission computed tomography/computed tomography; MRI=magnetic resonance imaging; PD=progressive disease.

Note: See Table 3 for detailed guidance on tumour assessment procedures.

a. Participants who have a PR or CR while on treatment and discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.

2. INTRODUCTION

Childhood cancers are a leading cause of death in children globally, with approximately 300 000 cancers diagnosed per year and an estimated 80 000 cancer-related deaths in children per year worldwide (IARC, 2017). Advancements in cancer therapies have improved survival over the last few decades, but survival rates have plateaued over the last 5 years for difficult-to-treat diseases such as acute myeloid leukaemia (AML), several central nervous system (CNS) tumours, neuroblastoma, and bone and soft tissue sarcomas. On average, approximately 20% to 30% of paediatric solid tumours will recur. The recurrence rate can be as high as 70% to 80% in specific tumour types, such as high-grade glioma. Based on literature review, the expected response rate at the time of relapse is approximately 10% to 20% across these tumour types. This leaves a significant unmet medical need for the treatment of recurrent solid tumours in the paediatric population.

2.1. Background on Niraparib

Niraparib is a potent and selective inhibitor of poly (adenosine diphosphate-ribose) polymerase (PARP)1 and PARP2, which are key enzymes in the repair pathway for single-strand DNA breaks called base excision repair. When the activities of PARP1 and PARP2 are inhibited, single-strand DNA breaks become double-strand DNA breaks following DNA replication. Cancer cells are consequently forced to rely on double-strand DNA break repair mechanisms, in particular homologous recombination DNA repair (HRR), for their survival and proliferation. Defects in HRR can be caused by genetic and epigenetic alterations to dozens of genes, including *breast cancer susceptibility gene (BRCA) 1* and *BRCA2*. PARP inhibitors are therefore capable of selectively killing a subset of cancer cells with deficiencies in HRR that are dependent upon an alternative DNA repair pathway: Base excision repair.

2.1.1. Clinical Data for Niraparib

The use of PARP inhibitors as selective anticancer agents is supported by both nonclinical data demonstrating that PARP inhibitors are more potent cytotoxic inducers in tumours with inactivation of *BRCA1/2* than they are in tumours with functional *BRCA*, as well as by clinical studies showing that PARP inhibitors exhibit antitumour activity in patients with certain types of cancer such as breast, ovarian, prostate, and pancreatic cancers, including, but not limited to, those with defined *BRCA* mutations (Gonzalez-Martin, 2019; Moore, 2019; Sachdev, 2019). In general, there are compelling data in multiple tumour types to support the efficacy of niraparib in *BRCA*-mutated cancers, and although clinical data outside of *BRCA* mutations are limited, there are encouraging preclinical and emerging clinical data to suggest that tumours with mutations in HRR genes or that are HRR deficient may also be highly sensitive to niraparib. In Study 213356 (formerly study PR305011C; NOVA), a pivotal Phase 3 trial in adult participants with platinum-sensitive, recurrent ovarian cancer, niraparib was observed to prolong progression-free survival (PFS) relative to placebo across cohorts of participants with germline *BRCA* mutations (hazard ratio [HR]=0.27, $p<0.001$), non-germline *BRCA* mutations (HR=0.45, $p<0.001$), and non-germline *BRCA* mutations and HRR deficiencies (HR=0.38, $p<0.001$) (niraparib IB [GSK document No. RPS-CLIN-053021]). These data

support the hypothesis that patients without genomic *BRCA* mutations may still benefit from niraparib treatment, and it is likely that the activity of niraparib in these patients is driven by defects in HRR other than *BRCA* mutations.

As of December 2023, niraparib is approved in over 40 countries worldwide, including the US, European Union, Japan, China, Switzerland, Australia, and Canada as maintenance treatment for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy and for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete response (CR) or PR to first-line platinum-based chemotherapy.

2.2. Background on Dostarlimab

Dostarlimab is a humanised monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) subclass that binds with high affinity to programmed cell death protein 1 (PD-1) and blocks the interaction between PD-1 and its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2).

PD-1 is a cell surface receptor expressed on T cells that limits T-cell activation through binding to PD-L1 and, to a lesser extent, PD-L2 (Dong, 1999; Freeman, 2000; Ishida, 1992; Latchman, 2001; Tseng, 2001). The PD-1/PD-L1 checkpoint serves as a negative regulator of T-cell activity to help control local inflammatory responses and maintain self-tolerance. PD-L1 is expressed constitutively on a subset of macrophages, but it is also known to be expressed on tumour cells (Keir, 2008). In the tumour microenvironment, when PD-L1 on tumour cells binds to PD-1 on activated T cells, T-cell activation is inhibited, which prevents tumour cell killing by T cells (Chen, 2015; Zou, 2008). This process is called immune evasion. Blockade of the interaction between PD-1 and PD-L1/PD-L2 with dostarlimab in patients with solid tumours is expected to strengthen the functional activity of tumour-infiltrating lymphocytes and promote tumour cell death.

Dostarlimab was generated using a proprietary platform that employs affinity maturation to select highly specific antibodies with desired functional characteristics (Bowers, 2011). The functional antagonist activity of dostarlimab was confirmed in a mixed lymphocyte reaction, demonstrating enhanced activation of T cells as measured by interleukin-2 production upon the addition of dostarlimab (Laken, 2016).

2.2.1. Clinical Data for Dostarlimab

Dostarlimab was granted accelerated approval by the United States Food and Drug Administration (FDA) on 22 April 2021 with subsequent conversion to a full approval on 09 February 2023 for the treatment of adult patients with mismatch repair-deficient (dMMR) recurrent or advanced endometrial cancer, as detected by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen (Biologics License Application [BLA] 761,174). A Conditional Marketing Authorisation Application (CMAA) was granted by the European Medicines Agency (EMA) on 21 April 2021 with subsequent conversion to a full approval on 07 December 2023 for use in women with dMMR/microsatellite instability-high (MSI-H) recurrent or

advanced endometrial cancer, who have progressed on or following prior treatment with a platinum-containing regimen. In addition, accelerated approval was granted by the FDA on 17 August 2021 for dostarlimab for the treatment of patients with recurrent or advanced dMMR solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options (BLA 761, 223)

The US and European approvals were based on data from GSK study 213346 (formerly study 4010-01-001; GARNET), which evaluated dostarlimab monotherapy in participants with recurrent or advanced solid tumours who have limited treatment options and who had dMMR/microsatellite-instability-high endometrial cancer that progressed on or after a platinum-containing regimen. An objective response rate (ORR; blinded independent review using Response Evaluation Criteria in Solid Tumours [RECIST] v1.1) of 44.7% (95% CI: 34.9, 54.8) was observed (dostarlimab IB (GSK document No. RPS-CLIN-029721).

2.3. Rationale for Synergy Between PARP Inhibitors and Immune Checkpoint Inhibitors

There is a strong preclinical rationale, as well as emerging clinical data, for synergy between PARP inhibitors and immune checkpoint inhibitors. It has been demonstrated that PARP inhibitors increase lymphocyte infiltration and activation in mouse tumour models (Huang, 2015) turning “immunologically cold” tumours into “immunologically hot” tumours, which are more likely to respond to anti-PD-1 therapies.

Both intrinsic DNA repair deficiency and PARP inhibition lead to accumulation of DNA damage and cytoplasmic DNA, which leads to activation of the stimulator of interferon genes (STING) pathway (Ding, 2018; Hartlova, 2015; Parkes, 2017). The STING pathway in turn contributes to antitumour immune responses in cancer [reviewed in (Barber, 2015; Li, 2018)].

Recently, PARP inhibitors have been shown to elevate PD-L1 expression (Jiao, 2017). This finding suggests that the immunomodulatory effects of PARP inhibitors could be muted by the expression of PD-L1, and that blocking PD-1 or PD-L1 may enhance the ability of niraparib to induce durable responses. Nonclinical studies conducted in syngeneic murine models have demonstrated the increased efficacy of an anti-PD-1/niraparib combination over either agent alone, and the combination was well tolerated in these studies (Huang, 2015; Meade, 2016; Mills, 2017; Xing, 2006).

Finally, in Study 213363 (formerly study 3000-PN162-01-001; TOPACIO) in adults with platinum-resistant ovarian cancer and triple-negative breast cancer, the combination of niraparib and an anti-PD-1 inhibitor (pembrolizumab) demonstrated efficacy in a broad range of biomarker-defined subpopulations including those participants with normal *BRCA* alleles and without molecular evidence of HRR deficiency, with improved activity as compared to either agent alone (Vinayak, 2019). Safety data were consistent with the safety profiles described for either treatment as monotherapy. Furthermore, the combination was shown to be tolerable with no new safety signals identified (Konstantinopoulos, 2017). The incidence of immune-related TEAEs with dostarlimab

was comparable to that observed with pembrolizumab, dostarlimab and pembrolizumab have the same molecular target and therefore mechanism of action, and results from GARNET suggest the safety and efficacy of dostarlimab are comparable to those of pembrolizumab. Niraparib is currently being investigated in combination with dostarlimab in several adult disease settings, including a registrational study (Study 213359; formerly study 3000-03-005; FIRST) evaluating maintenance with niraparib and dostarlimab as part of a treatment plan following first-line treatment in adult participants with either Stage 3 or 4 nonmucinous epithelial ovarian cancer.

2.4. Rationale for Tumour Type

The tumour types that are targeted for niraparib clinical development in adults (eg, ovarian, breast, prostate, and lung cancer) do not occur or are extremely rare in children. In paediatric malignancies, mutations in the HRR pathway are infrequent (Harttrampf, 2017), and there is no single tumour type that would be characteristic of these mutations. However, there are other mechanisms that could lead to deficiency in HRR, thereby predisposing the tumour to respond to PARP inhibitors. A method to identify tumours with homologous recombination deficiency is through genome-wide mutational signature. An example of one of these mutational signatures is mutational signature 3, present in a relatively high percentage of paediatric solid tumours across multiple tumour types (Gröbner, 2018). Mutational signature 3, also henceforth referred to as *BRCA*ness mutational signature, in turn has been linked with the failure of double-strand DNA break repair by HRR (Alexandrov, 2013). Based on a recent report of whole genome sequencing of over 500 paediatric tumours, the following tumour types exhibit the *BRCA*ness mutational signature in approximately >50% of cases: Osteosarcoma, adrenocortical carcinoma, neuroblastoma, medulloblastoma, high-grade glioma, rhabdomyosarcoma (Gröbner, 2018; Kovac, 2015, PedPanCan), and Ewing sarcoma (personal communication with Dr Stefan Pfister, 16 May 2018). Osteosarcoma and neuroblastoma, specifically, exhibit the *BRCA*ness mutational signature in >90% of cases (Gröbner, 2018). Additionally, nonclinical data support the rationale for PARP inhibitor activity not necessarily related to the presence of mutational signature 3 in many of the aforementioned tumour types, including osteosarcoma (Chornenkyy, 2015; Engert, 2017; Engert, 2015; Garnett, 2012; Kovac, 2015; Smith, 2011). CCI [redacted]

2.5. Rationale for Current Study

Historically, the response rates observed in early-phase studies of single agents used to treat relapsed paediatric tumours are lower than the response rates observed using combination therapies (Waligora, 2018). Data on the activity of single agent PARP inhibitors in paediatric tumours hold limited promise (Choy, 2014; Chugh, 2017; Federico, 2017). Combining PARP inhibitors with cytotoxic chemotherapy has been limited by overlapping toxicity profiles that result in intermittent dosing of the PARP

inhibitors, which may reduce their efficacy (Chen, 2016; Chugh, 2017; Halford, 2017; Kurzrock, 2014). On the other hand, combining PARP inhibitors with biologic agents has been well tolerated and has allowed dosing of the PARP inhibitor at the single agent maximum tolerated dose (MTD) level (Dean, 2012; Konstantinopoulos, 2017; Lee, 2017; Liu, 2013; Mirza, 2017). The activity of immune checkpoint inhibitors in paediatric solid tumours as a single agent has also been limited (Geoerger, 2017; Kabir, 2018; Kara L. Davis, 2017). The activity of immune checkpoint inhibitors in adult indications has been linked to the expression of PD-L1 in the tumour as well as to the overall TMB. Similar to the *BRCA*ness mutational signature, there is no single histologic subtype of paediatric tumours with high TMB (Gröbner, 2018) or PD-L1 expression (Geoerger, 2017). However, tumour types with these attributes, such as osteosarcoma, high-grade glioma, rhabdomyosarcoma, adrenocortical carcinoma, medulloblastoma, and neuroblastoma, overlap with tumours with a high *BRCA*ness mutational signature (Geoerger, 2017; Gröbner, 2018).

This initial clinical study in the paediatric population will therefore evaluate the combination of a PARP inhibitor, niraparib, with the PD1 inhibitor, dostarlimab. The study will be conducted to determine the recommended Phase 2 dose (RP2D) and evaluate the pharmacokinetics (PK), safety, and efficacy of niraparib in combination with dostarlimab in paediatric participants ≥6 months to <18 years of age with recurrent or refractory solid tumours that are known to have CCI [redacted] The study will be conducted as a two-part dose escalation, followed by Cohort Expansion. In Part 1A, the RP2D of the niraparib tablet formulation and dostarlimab will be determined, unless the need arises for use of the tablet for oral suspension CCI of niraparib for evaluation of a lower dose. Part 1B will determine the PK parameters of the CCI of niraparib in combination with dostarlimab, with the objective of determining the RP2D of the niraparib CCI in combination with dostarlimab for the intended paediatric population (i.e., participants not able to swallow the tablet formulation). Part 2 will consist of disease-specific expansion cohorts of participants, including participants with osteosarcoma or neuroblastoma, to evaluate the anticancer activity of the RP2D of niraparib and dostarlimab. The details for Part 2 of this study are presented in each cohort-specific supplement, as applicable.

2.6. Benefit Risk Assessment

2.6.1. Risk Assessment:

2.6.1.1. Niraparib Monotherapy

More detailed information about the known and expected risks and reasonably expected adverse events (AEs) of niraparib observed in adults may be found in the current version of the niraparib Investigator's Brochure (niraparib IB (GSK document No. RPS-CLIN-053021). Risk minimisation measures for this study (such as dose reduction and discontinuation) are discussed in Table 5, Section 4.7.2.1 (including Table 9 and

Table 10), and Section 6.8.1. The SoA table in Section 1.3 also indicates safety follow-up visits.

Table 5: Summary of Risks and Mitigations for Niraparib

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Thrombocytopenia Anaemia Neutropenia including neutropenic infection and sepsis.	Based on nonclinical and clinical observations as well as identified risk with PARP inhibitor, niraparib	Protocol provides guidelines for monitoring haematologic labs and adverse reactions (Section 4.7.2.1, Table 10) Protocol provides guidance for dose modification and discontinuation of study (Section 4.7.2.1, Table 10)
Hypertension	Cases reported with niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment (Section 4.7.2.1, Table 9)
MDS or AML, along with other second primary malignancy (new malignancies other than MDS or AML)	Based on nonclinical and clinical observations as well as identified with PARP inhibitor, niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment (Section 4.7.2.1, Table 10)

Abbreviation: AML=Acute myeloid leukaemia; MDS=Myelodysplastic syndrome; PARP=poly (adenosine diphosphate-ribose) polymerase.

2.6.1.2. Dostarlimab Monotherapy

More detailed information about the known and expected risks and reasonably expected AEs of dostarlimab observed in adults may be found in the current version of the dostarlimab Investigator's Brochure (GSK document No. RPS-CLIN-029721). Risk minimisation measures for this study (such as dose reduction and discontinuation) are discussed in Table 6, Section 4.7.2.2 (including Table 11), and Section 6.8.1. The SoA table in Section 1.3 also indicates safety follow-up visits.

Table 6: Summary of Risks and Mitigations for Dostarlimab

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
Immune-mediated AEs (imAEs; including pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other imAEs)	imAEs, which may be severe or fatal, can occur in patient treated with monoclonal antibodies directed against immune checkpoints, including dostarlimab. While imAEs usually occur during treatment, symptoms can also manifest after discontinuation of treatment. imAEs may occur in any organ or tissue and may affect more than one body system simultaneously.	Participants with the following medical history are ineligible for this study: • Toxicity related to prior immunotherapy leading to study treatment discontinuation • Active autoimmune disease • Severe hypersensitivity to dostarlimab, its components, or its excipients. Established management algorithms for imAEs: refer to Table 11 and Table 12 for further details on the identification, evaluation, and management of toxicities, including cumulative effects, with a potential immune etiology.

Abbreviations: AE=adverse event; imAE=immune-mediated adverse event; IRR=infusion-related reaction; mAb=monoclonal antibody; PD-(L)1=programmed cell death protein 1/(programmed death-ligand 1).

2.6.1.3. Niraparib plus Dostarlimab Combination Safety and Efficacy

In addition to current paediatric study 213406, GSK is evaluating the efficacy and safety of dostarlimab in combination with niraparib in the following studies in adults:

- Study 213357 (OPAL, formerly known as 3000-02-005): A Phase 2 multicohort study to evaluate the safety and efficacy of novel treatment combinations (niraparib at 300 mg or 200 mg plus dostarlimab in combination with bevacizumab) in patients with recurrent ovarian cancer (NCT03574779).
- Study 213361 (RUBY, formerly known as 4010-03-001): A Phase 3 multicohort study to evaluate dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel in participants with recurrent or primary advanced endometrial cancer. Part 2 includes participants receiving dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib (NCT03981796).

GSK evaluated the efficacy and safety of dostarlimab in combination with niraparib in the following studies in adults:

- Study 213351 (IOLite, formerly known as 3000-01-002): A Phase 1b dose finding study of niraparib, cobolimab, bevacizumab, and platinum-based doublet chemotherapy in combination with dostarlimab in patients with advanced or metastatic cancer. Two parts of the study (Part A and C) include niraparib and evaluated the safety and preliminary efficacy of niraparib in combination with dostarlimab or niraparib plus bevacizumab in combination with dostarlimab in patients with advanced or metastatic cancer (NCT03307785).
- Study 213352 (JASPER, formerly known as 3000-02-001): A Phase 2, multiarm study of niraparib administered alone and in combination with a PD-1 inhibitor (pembrolizumab or dostarlimab) in patients with non-small cell lung cancer (NCT03308942).
- Study 213353 (MOONSTONE, formerly known as 3000-02-006): A Phase 2 open-label, single-arm study to evaluate the efficacy and safety of the combination of niraparib and dostarlimab in patients with platinum-resistant ovarian cancer (NCT03955471).
- Study 213355 (FIRST, formerly known as 3000-03-005): A randomised, double-blind, Phase 3 comparison of platinum-based therapy with dostarlimab and niraparib versus standard of care platinum-based therapy as first-line treatment of Stage III or IV non-mucinous epithelial ovarian cancer (NCT03602859).

Safety

As of March 2023, the safety and tolerability of niraparib has been evaluated in >2000 participants with advanced cancers who have received at least 1 dose of niraparib, of whom over 250 received niraparib in combination with a PD-1 inhibitor (either dostarlimab or pembrolizumab) (niraparib IB [GSK document No. RPS-CLIN-053021]). As expected, considering the well-established safety profile of PD-1 inhibitors, including dostarlimab and pembrolizumab, and the safety profile of niraparib, no new safety signals were observed with the combination of niraparib and a PD-1 inhibitor. Overall, the safety profiles observed to date are consistent with the safety profile of either niraparib or dostarlimab monotherapy.

Efficacy

Niraparib and Dostarlimab

Efficacy results from the IOLite study demonstrated clinical benefit with the treatment combination of dostarlimab and niraparib. Although the sample size was small, encouraging preliminary evidence of antitumour activity was demonstrated in the participants treated with dostarlimab in combination with niraparib. In general, pharmacokinetic (PK) analysis following administration of dostarlimab plus niraparib showed no appreciable differences in systemic exposure between treatments.

Niraparib and Pembrolizumab

Efficacy has also been demonstrated for niraparib in combination with the PD-1 inhibitor pembrolizumab (a PD-1 inhibitor compared to which dostarlimab is proposed to have similar safety and activity characteristics) in the TOPACIO (Study 213363) and JASPER

(Study 213352) studies. In the TOPACIO study, the combination demonstrated antitumour activity across biomarker-defined subpopulations including patients with normal *BRCA* alleles and without molecular evidence of HRR (Konstantinopoulos , 2017; Vinayak 2019). Furthermore, the combination was shown to be tolerable with no new safety signals identified (Konstantinopoulos , 2017; Vinayak , 2019).

The JASPER study also demonstrated antitumour activity in adults with non-small cell lung cancer with the combination of niraparib and pembrolizumab with the highest response rate observed in participants with high PD-L1 expression (Ramalingam, 2022; GSK document No. RPS-CLIN-053021). Like TOPACIO, the combination was tolerable and no new safety signals were observed.

2.6.2. Overall Benefit: Risk Conclusion

As demonstrated in the NOVA study for monotherapy niraparib and in the GARNET study for monotherapy dostarlimab, clinical evidence supports a positive risk/benefit profile for each agent individually when used as monotherapy. Both agents have displayed antitumour activity and have manageable safety profiles that are well-established by extensive clinical trial and post-marketing experience. Clinical evidence on the combination of niraparib and dostarlimab in the adult population demonstrates a manageable safety profile with signs of synergistic activity in refractory/recurrent adult populations irrespective of mutational status. Antitumour activity has been reported from IOLite for the combination of niraparib plus dostarlimab and from TOPACIO for the combination of niraparib and pembrolizumab in the targeted patient populations.

In summary, the available efficacy and safety evidence from the combination of niraparib and dostarlimab in the adult population suggests potential therapeutic benefit for the treatment of recurrent solid tumours in the paediatric population. Therefore, it is warranted to explore the safety and efficacy of the combination at the appropriate dose as determined in the planned Part 1 in a trial of paediatric participants with high unmet medical need.

Information from this study will inform the Sponsor of the safety, tolerability, and initial signs clinical activity of the proposed combination in the specified tumour types.

2.6.3. Dose Justification

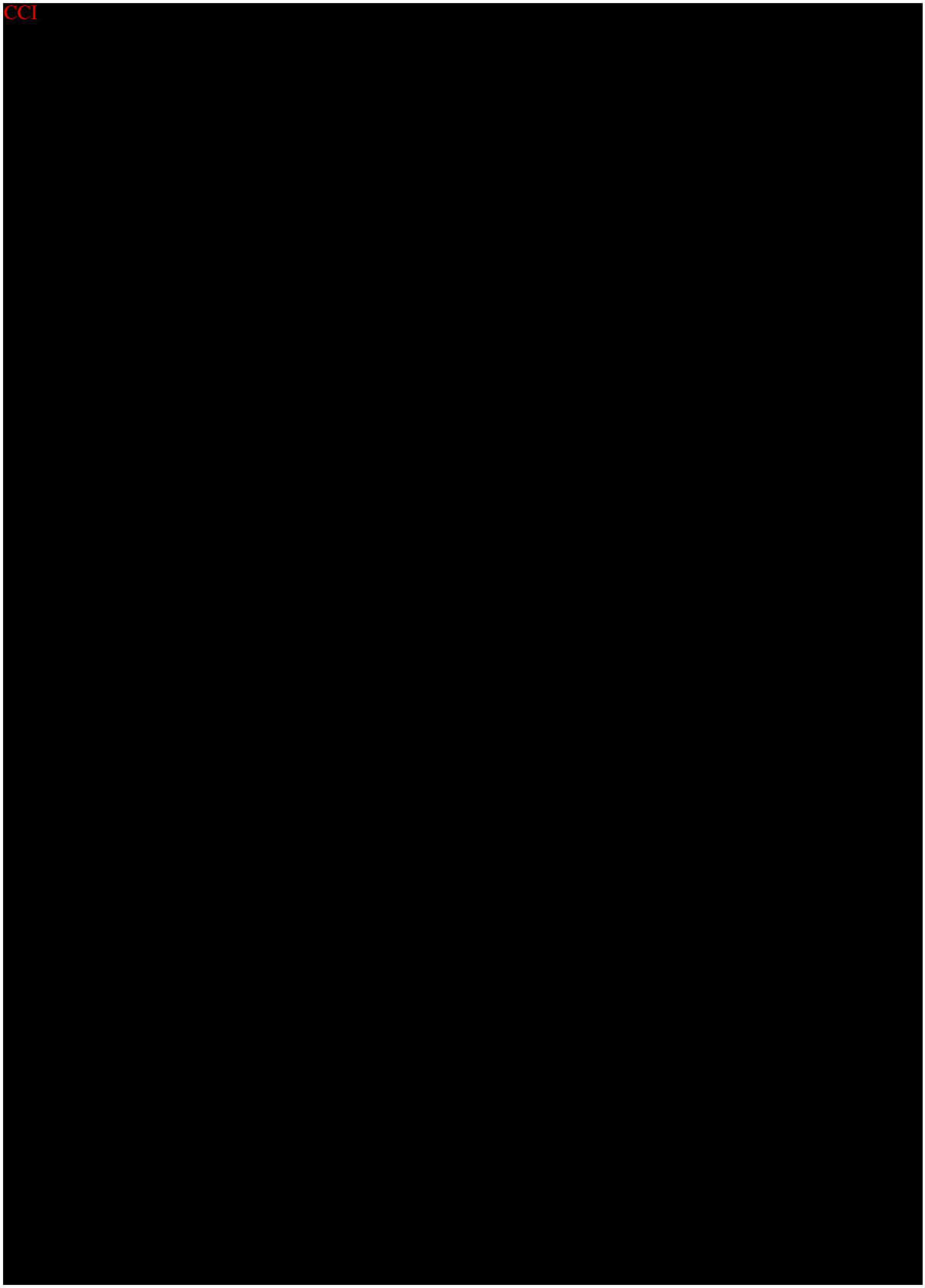
2.6.3.1. Niraparib Dosing

Niraparib Dosing in Adults

The recommended dose of CCI [redacted] for first-line maintenance treatment of ovarian cancer is CCI [redacted] for participants weighing <77 kg or with a platelet count <150 000/µL or CCI [redacted] for participants weighing ≥77 kg and with a platelet count ≥150 000/µL based on the PRIMA study. The recommended dose for second-line maintenance treatment of ovarian cancer is CCI [redacted]. In univariate exposure-response analyses of the PRIMA study, increasing niraparib exposure was associated with increasing risk of thrombocytopenia, anaemia, neutropenia, hypertension, and fatigue AEs.

Niraparib Dosing in Children

CCI



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[redacted]

2.6.3.2. Dostarlimab Dose

Dostarlimab Dosing in Adults

The currently approved adult dosing regimen for CCI [redacted] for subsequent cycles until disease progression or unacceptable toxicity based on study 213346 (GARNET) for endometrial cancer in the US and EU and dMMR pan-tumour in the US.

Based on exposure-response analysis of the data from the GARNET study, there was no statistically significant relationship between dostarlimab PK exposure (area under the plasma concentration-time curve [AUC], maximum plasma concentration [Cmax], and minimum plasma concentration [Cmin] during the first dosing interval [21 days]) and overall response rate after accounting for patient and disease-related covariates. From the exposure-safety analysis, dostarlimab PK exposures (AUC, Cmax, and Cmin) during the first 6 weeks after the first dose (i.e., 42 days) did not have a statistically significant or clinically relevant relationships with any of the 5 most prevalent drug-related AEs as assessed by Investigators (asthenia, diarrhoea, fatigue, hypothyroidism, and nausea) (dostarlimab IB GSK Document No. RPS-CLIN-029721).


CCI

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints for Part 1 of this study are detailed as follows in Table 8. The study design and endpoints for Part 2 of this study are detailed in the separate cohort-specific supplements; however, the common objectives are summarised as follows in Table 8.

Table 8: Objectives and Endpoints for Study 213406

Objectives	Endpoints
Primary	
Part 1A: Establish the RP2D of the combination of niraparib tablet and dostarlimab in paediatric participants	Assess the incidence of DLTs by study part and cohort for the DLT-evaluable Population.
Part 1B: Establish the RP2D of the combination of CCI [redacted] in paediatric participants	Assess the incidence of DLTs by study part and cohort for the DLT-evaluable Population.
Part 2: Assess the safety, tolerability, and the antitumour activity of the combination of niraparib and dostarlimab	*Please refer to the separate cohort-specific supplements for this information.*
Secondary	
Evaluation of measures of anticancer activity in paediatric participants	ORR based on Investigator assessment is defined as the proportion of participants with a BOR of confirmed CR or PR as determined by the Investigator using RECIST v1.1 or INRC (for participants with neuroblastoma only). DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 or INRC (for participants with neuroblastoma only) based on Investigator assessment or death (whichever occurs first). *Part 2: Please refer to the separate cohort-specific supplements for this information.*
Evaluation of the safety and tolerability of the combination of CCI [redacted] in paediatric participants	Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
Characterisation of the PK of the combination of niraparib and dostarlimab in paediatric participants	Niraparib and dostarlimab concentrations; PK parameters of niraparib and dostarlimab, if appropriate.

Objectives	Endpoints
Assessment of the immunogenicity of dostarlimab in paediatric participants	Rate and extent of ADA to dostarlimab.
CCI	
Exploratory	
CCI	

Abbreviations: ADA=antidrug antibody(ies); AE=adverse event; BOR=best overall response; CR=complete response; CCI ; DLT=dose limiting toxicity; DOR=duration of response; INRC=International Neuroblastoma Response Criteria; imAE=immune-mediated adverse event; ORR=objective response rate; PD=progressive disease; PK=pharmacokinetic(s); PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; RP2D=recommended Phase 2 dose; SAE=serious adverse event; SoA=schedule of activities; TEAE=treatment-emergent adverse event; CCI

4. OVERALL DESIGN

This is a master protocol for a Phase 1, multicentre, open-label, dose escalation study (Part 1) with a Safety Run-in and Cohort Expansion component (Part 2) (Figure 1). The study will consist of an initial dose escalation portion conducted in participants with tumours that are known to have a CCI [redacted] Part 1A, a dose escalation to determine the RP2D of the combination of niraparib tablets and dostarlimab, included participants who were able to swallow the CCI [redacted] niraparib tablets and who had a body weight of ≥20 kg. Part 1B, a dose escalation to determine the RP2D of the combination of CCI [redacted], under Protocol Amendment 03 (or earlier), included participants who could not swallow the CCI [redacted] or who had a body weight of <20 kg. In Part 2 of the study under Protocol Amendment 03, the RP2D regimen established in Part 1 was evaluated for efficacy and safety in disease-specific expansion cohorts including participants ≥20 kg and able to swallow CCI [redacted]. Under Protocol Amendment 05, participants will receive CCI [redacted], and eligibility for Part 1B is no longer dependent upon participant weight or ability to swallow niraparib tablets. Instead, CCI [redacted]

A review of safety data and available preliminary PK data will be conducted by the Sponsor and Investigators following completion of the DLT observation periods in Part 1A, Part 1B, and the Part 2 Safety Run-in. Determination of the specific RP2D will be based on review of safety and PK data. An mTPI-2 dose escalation design will be used for the evaluation of safety at each dose level (Appendix 10).

CCI [redacted] Otherwise, participants requiring a niraparib dose reduction from CCI [redacted] were to be required to discontinue study treatment (both drugs).

The study designs for the Part 2 Safety Run-in and for the Part 2 expansion cohorts are described in each of the cohort-specific supplements.

4.1. Part 1 Dose Escalation Design

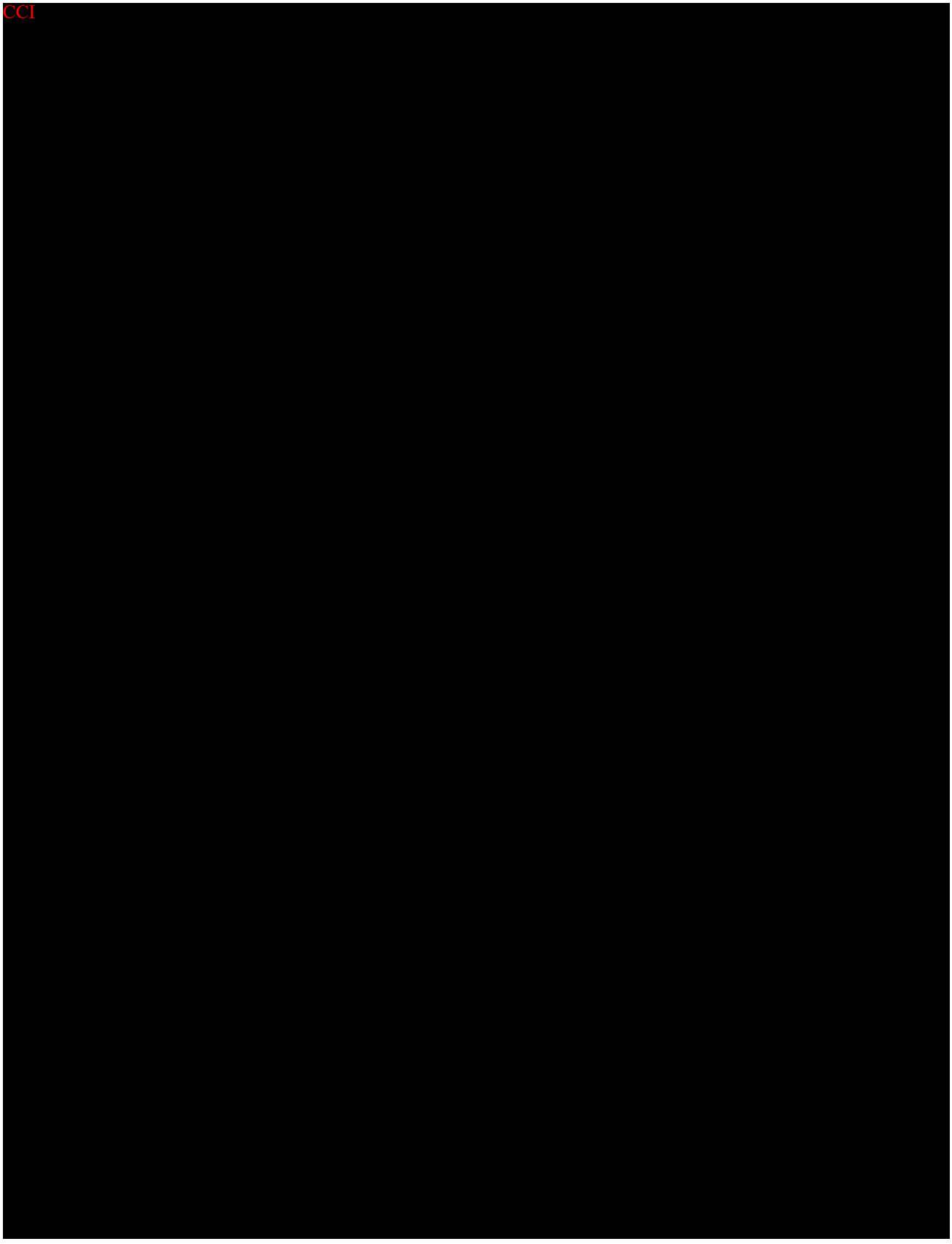
CCI [redacted]

CCI [redacted]

4.1.1. Part 1A Design

CCI [redacted]

Participants in Cohort 0 were dosed in a staggered fashion. At this dose level, no more than 3 participants were allowed to receive an initial dose of study treatment until the first 3 participants had all completed at least 1 cycle of study treatment and the resulting data from all 3 participants had been reviewed. This was to ensure an adequate interval for observation and assessment of potential acute AEs. Although not needed, dosing strategy for subsequent participants after the initial 3 participants dosed was to have been made by the Dose Escalation Committee (DEC) if >1 DLT was observed in the first 3 participants within the first cycle of treatment for each participant (see Appendix 1 for details regarding the DEC).


CCI

If Cohort 0 CCI was deemed safe based on the mTPI-2 parameters described above, 2 cohorts were to have opened: Cohort 1A and Cohort 1B. In Cohort 1A, CCI In Cohort 1B, niraparib was to be escalated to dose level 2 (DL2; no more than 2 times DL1) as determined based on the observed DLTs and PK values, if available, from Cohort 0, and CCI. If both Cohorts 1A and 1B were considered safe, then Cohort 2 CCI was to be opened. If the Cohort 2 dose level was deemed safe, this ***may have been*** considered the RP2D for the niraparib tablet formulation. If the dose level from Cohort 2 was not cleared for use, the RP2D was to be the dose level from Cohort 1B. If only 1 cohort of Cohorts 1A and 1B was deemed safe, then that dose level was to be considered the RP2D. Lastly, if neither Cohort 1A nor 1B was deemed safe, the combination dose level from Cohort 0 was to be the RP2D.

If Cohort 0 was deemed too toxic based on the mTPI-2 parameters described above, a clinical assessment of the observed DLTs was to be done. If it was determined by the Sponsor and the Site Investigators that all the DLTs observed could be attributed to an immune checkpoint inhibitor (ICI), Cohort -1A, CCI, was to be opened (Figure 3, B. Dose De-escalation). If not all DLTs observed could be attributed to an ICI, Cohort -1B, with niraparib de-escalated to dose level -1 (DL-1; determined based on the observed PK data in Cohort 0 and availability of an alternative dosing option[s], including the TfOS) and dostarlimab CCI, was to be opened.

If Cohort -1A CCI was deemed safe based on the mTPI-2 parameters described above, the dose level from Cohort -1A was to be established as the RP2D. If Cohort -1A was not cleared and it was determined by the Sponsor and the Site Investigators that all the DLTs observed could be attributed to an ICI, the study would not continue as designed. If Cohort -1A was not cleared and it was determined by the Sponsor and the Site Investigators that not all the DLTs observed could be attributed to an ICI, Cohort -2, evaluating niraparib at DL-1 and dostarlimab at 1 mg/kg Q3W, would be opened. If Cohort -2 was deemed safe, the dose level from Cohort -2 would be the RP2D. If Cohort -2 was not cleared, the study would not continue as designed. Alternate dosing option(s), such as use of a lower dose with the TfOS, may also have been implemented for niraparib, if appropriate.

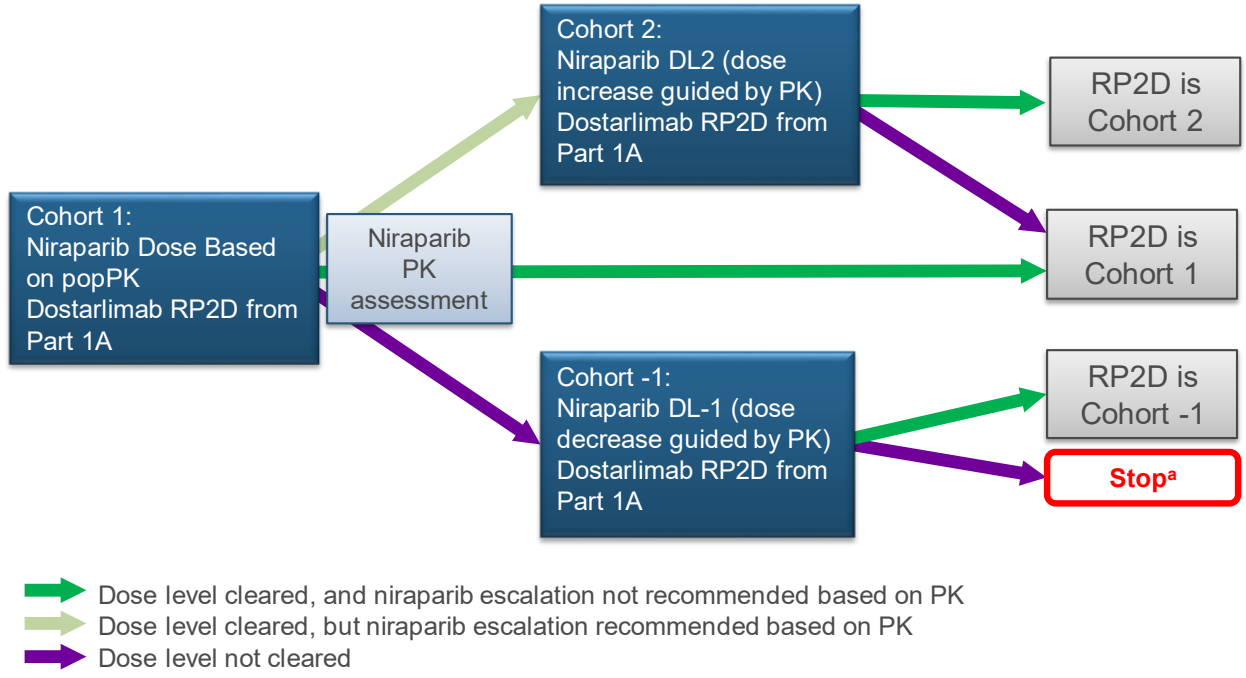
If Cohort -1B CCI was deemed safe based on the mTPI-2 parameters described above, the dose level from Cohort -1B was to be established as the RP2D. If Cohort -1B was not cleared and it was determined by the Sponsor and the Site Investigators that all the DLTs observed could be attributed to an ICI, Cohort -2 evaluating CCI, was to be opened. If Cohort -1B was not cleared and it was determined by the Sponsor and the Site Investigators that not all the DLTs observed could be attributed to an ICI, the study would not continue as designed. If Cohort -2 was deemed safe, the dose level from Cohort -2 was to be considered the RP2D. If Cohort -2 was not cleared, the study would not continue as designed. Alternate dosing option(s), such as use of a lower dose with the TfOS, may also have been implemented for niraparib, if appropriate.

Once the RP2D of niraparib and dostarlimab was established in Part 1A for CCI [redacted], Part 2 (disease-specific expansion cohorts, as described in cohort-specific supplements to this protocol) was opened to accrual for a limited number of participants who were able to swallow the CCI [redacted]. In addition, Part 1B opened once the RP2D was established in Part 1A and the niraparib TfOS was available (Section 4.1.2).

4.1.2. Part 1B Design

CCI [redacted]

Figure 4: Part 1B Study Schema Under Protocol Amendment 03 (or Earlier)



Abbreviations: DL-1=dose level -1; DL2=dose level 2; PK=pharmacokinetic(s); popPK=population pharmacokinetics; RP2D=recommended Phase 2 dose.

a. The study will not continue as designed. Alternate niraparib schedules (such as dosing during 2 of 3 weeks) and/or conversion to body surface area-based dosing may also be implemented for niraparib, if appropriate.

Following the enrolment pause and review and analysis of clinical, safety and PK data for all study participants, Part 1B will restart using a modified CCI [redacted] described in Section 2.6.3.1 and Table 7. CCI [redacted]

The planned dose escalation schema for the reopened Part 1B is in Figure 5. PK evaluations will be performed in at least 6 participants in each cohort unless enrolment into the cohort is closed prematurely due to toxicity.

CCI [redacted]

Enrolment into each Part 1B cohort will take participant age into consideration, with the intent to distribute enrolment across 3 age categories: 6 months to <2 years; ≥2 years to <6 years; and ≥6 years to <8 years. Enrolment into each cohort will be limited to no more than 4 participants aged 6 years or older out of the first 6 participants. The remaining 2 participants out of the first 6 participants in each cohort must be younger than age 6 years.

Once enrolment into Cohort A has reached the target 6 participants (or 8, if necessary), safety and PK data will be evaluated, and the decision will be made to open either Cohort B or Cohort C. Decision steps are described below.

If Cohort B is to be opened, but at least 1 participant from the youngest age category (6 months to <2 years) has not been enrolled in Cohort A, the first potential participant aged 6 months to <2 years to join the study will be enrolled into Cohort A to permit safety evaluation of the starting niraparib and dostarlimab dose levels. Data from this ≥6

months to <2 years of age participant will not contribute to the decision for the next dose level, but may be used to evaluate safety and PK within that age category.

The DEC will review all relevant safety and PK data immediately after all participants treated in the same dose cohort have passed the DLT period. For Cohort A, the DEC may potentially initiate data review as soon as 2 participants have been enrolled and observed for the DLT period, depending on the occurrence of DLTs and/or Grade ≥3 thrombocytopenia.

Cohort A

Participants in Cohort A will be dosed in a staggered fashion, meaning, no more than 2 participants will be allowed to receive the initial dose of study treatment until each participant has completed 2 cycles of study treatment and the resulting clinical safety data from both participants have been reviewed. This is to ensure an adequate interval for observation and assessment of tolerability of the dose.

- If DLTs or Grade ≥3 thrombocytopenia are observed in ≤1 of the first 2 dosed participants and it is deemed safe to proceed by the study team, a third participant will be allowed to receive the initial dose of study treatment. No additional participants will be allowed to receive study treatment until the third participant has completed at least 2 cycles of study treatment and the resulting data have been reviewed by the study team.
- If DLTs or Grade ≥3 thrombocytopenia are observed in <2 of the first 3 dosed participants, Cohort A will continue to enrol up to 6 evaluable participants. If a DLT is observed in 2 of the first 6 dosed participants, Cohort A will be expanded to 8 DLT-evaluable participants.
- If DLTs or Grade ≥3 thrombocytopenia are observed in both of the first 2 dosed participants, Part 1B will be paused. Safety data for the first 2 dosed participants will be reviewed by the DEC. The dosing strategy for subsequent participants will be determined by the DEC. (See Appendix 1 for details regarding the DEC.)
- If DLTs or Grade ≥3 thrombocytopenia are observed in 2 of the first 3 dosed participants, Part 1B will be paused and safety data and PK data will be reviewed by the DEC. The dosing strategy for subsequent participants will be determined by the DEC.
- If 8 participants have been enrolled and if DLTs are observed in 3 or more of 8 DLT-evaluable participants, the dose level will not be cleared and the decision about the next dose level will be made by the DEC (i.e., to proceed to Cohort C with niraparib DL-1).

If Cohort A is deemed safe based on the mTPI-2 parameters described previously, results of the niraparib PK assessment will be taken into consideration when determining the RP2D. If the PK exposure for the niraparib TfOS is consistent with the exposure observed in adults, the niraparib dose in Cohort A will be the basis of determining the RP2D for the TfOS.

If the PK exposure for dostarlimab in Cohort A is consistent with the exposures observed in adults, then the dose level of niraparib and of dostarlimab from Cohort A will be determined to be the RP2D.

If the PK exposures observed in Cohort A with the niraparib TfOS are substantially lower than those observed in adults, a dose escalation cohort (Cohort B) will be opened.

Cohort B

The dose of niraparib for Cohort B will be determined based on the PK evaluation in Cohort A and the dose level of dostarlimab will remain the same as in Cohort A.

If Cohort B is deemed safe based on the mTPI-2 parameters, results of the niraparib PK assessment in Cohort B will be taken into consideration when determining the RP2D for TfOS.

If the PK exposure for the niraparib TfOS in Cohort B is consistent with the exposures observed in adults, the niraparib dose in Cohort B will be the basis of determining the RP2D for the TfOS.

Cohort C

If Cohort A is not cleared based on the mTPI-2 parameters described above, Cohort C will be opened using a reduced niraparib dose, determined based on the niraparib PK evaluation in Cohort A. The dose of dostarlimab will be the same as in Cohort A.

If Cohort C is deemed safe based on the mTPI-2 parameters described above, results of the niraparib PK assessment in Cohort C will be taken into consideration when determining the RP2D for TfOS.

If the PK exposure for the niraparib TfOS in Cohort C is consistent with the exposures observed in adults, the niraparib dose in Cohort C will be the basis of determining the RP2D for the TfOS.

Cohort D

If the exposures of dostarlimab observed in Cohorts A and B (or Cohorts A and C) are substantially lower than those observed in adults, a dose escalation cohort (Cohort D) will be opened. The dose of dostarlimab for Cohort D will be determined based on the dostarlimab PK evaluation in Cohorts A and B (or Cohorts A and C). A dose of CCI [redacted] may be tested. The dose level of niraparib in Cohort D will be the niraparib RP2D as determined from evaluation in Cohorts A, B, and/or C.

If Cohort D is deemed safe based on the mTPI-2 parameters described above, the dose level of dostarlimab from Cohort D will be the RP2D in combination with the niraparib RP2D. If Cohort D is not cleared, then the dose level of CCI [redacted] from Cohort CCI [redacted] will be the RP2D in combination with the niraparib RP2D.

If Cohort C is not deemed safe, the study will not continue as designed.

Alternate niraparib schedules may be implemented for niraparib, if appropriate.

Additional dose levels of niraparib and/or dostarlimab may be evaluated based on safety and PK data from the specific cohorts. CCI [redacted]

Once the RP2D for the combination of the CCI [redacted] is determined in Part 1B of the study, participants <8 years of age will be eligible for enrolment into the Part 2 disease-specific expansion cohorts (described in cohort-specific supplements to this protocol).

In addition, once the RP2D is determined, the RP2D cohort in Part 1B will remain open until completion of Part 2 overall for additional enrolment to reach minimum N=3 participants enrolled in Part 1B RP2D within each age category: ≥6 months to <2 years; ≥2 years to <6 years; ≥6 years to <8 years.

4.2. Intra-Participant Dose Escalation

For participants who participate in Part 1A and 1B of the study, intra-participant dose escalation to a higher dose level of niraparib and/or dostarlimab that has been found to be safe during dose escalation may be allowed after all of the following have taken place:

a. participant has received at least 2 cycles of treatment in their current cohort
b. participant has required no dose modifications due to AEs
c. participant has no evidence of progressive disease (PD)
d. Investigator has determined that dose escalation would be in the best interest of the participant

Such cases must be discussed with the Sponsor.

4.3. Dose Limiting Toxicity

The DLT observation period is 42 days following the initiation of study treatment (ie, approximately the first 2 treatment cycles) in Part 1.

A participant will be considered unevaluable for DLT assessment if, for reasons other than DLT, the participant does not complete the DLT observation period or receives <80% of the intended niraparib dose (e.g., missed 9 or more doses; reason for missed doses may include, but is not limited to, noncompliance) or <2 infusions of dostarlimab.

Participants considered unevaluable may be replaced after consultation between the Sponsor and Investigator.

A participant may continue on study treatment following a DLT if the Investigator determines doing so is in the best interest of the participant, after discussion by the Investigator with the GSK Medical Monitor, and after appropriate recovery from the DLT by the participant.

DLT is defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related Grade 4 nonhaematologic clinical (nonlaboratory) AE.
- any treatment-related Grade 3 nonhaematologic clinical (nonlaboratory) AE not resolving to Grade ≤1 within 48 hours of initiating optimal medical intervention.
- any treatment-related Grade 3 or 4 nonhaematologic laboratory abnormality if any of the following also occur:
  - the abnormality leads to hospitalisation.
  - the abnormality persists for ≥7 days from the time of AE onset and participant is symptomatic from the AE and/or requires intervention.
- any treatment-related haematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for ≥7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding or requiring platelet transfusion.
  - Grade 4 neutropenia persists for ≥7 days, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥72 hours.
  - Grade 4 anaemia or Grade 3 anaemia requiring blood transfusion.
- any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2.
- any treatment-related toxicity resulting in the participant receiving <80% of the intended niraparib dose and/or <2 dostarlimab infusions due to dose modification/interruption/ reduction.
- any treatment-related Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks.
- any treatment-related Grade ≥2 immune-related endocrine toxicity that requires hormone replacement, except Grade 2 thyroiditis or thyroid dysfunction.
- any treatment-related Grade 2 colitis or diarrhoea that persists for ≥7 days without resolution to Grade ≤1 despite adequate steroid therapy.
- any Grade 3 or 4 imAE that does not resolve to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy.
- Grade 3 or higher infusion-related reaction.
- any grade of hemophagocytic lymphohistiocytosis.
- any grade of Posterior Reversible Encephalopathy Syndrome (PRES).
- any treatment-related Grade 5 AE.

4.4. General Study Conduct

This study consists of a Screening Period (Day -28 to Day -1), a Treatment Period, an End of Treatment (EOT) Visit, a Safety Follow-up Visit, and a Follow-up Assessment Period. During the Treatment Period, study treatment administration will occur in 3-week

cycles. Participants will receive niraparib daily or on an alternative schedule in combination with dostarlimab Q3W until documented PD, unacceptable toxicity, withdrawal of consent, Investigator's decision, or death.

Participants must have a baseline tumour assessment (computed tomography [CT] or magnetic resonance imaging [MRI]) of the chest, abdomen, pelvis, and any additional sites as clinically indicated within 28 days prior to the first dose of study treatment. Participants with neuroblastoma must also have a baseline tumour assessment via metaiodobenzylguanidine-single-photon emission computed tomography/computed tomography (MIBG-SPECT/CT) or fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) within 42 days prior to the first dose of study treatment. A baseline brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT) is required for participants with previously treated brain metastases. (Participants with previously treated brain metastases may participate under the conditions detailed in exclusion criterion 5 in this master protocol and in the exclusion criteria of each cohort-specific supplement for Part 2.)

Tumour assessments by CT or MRI of sites involved by disease at baseline and of any additional sites as clinically indicated will be done postbaseline, as will MIBG-SPECT/CT or FDG-PET/CT tumour assessments (participants with neuroblastoma only). Tumour assessments should be conducted every 9 weeks (every 63 [±7] days) for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, following the start of study treatment, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation of participant from overall study participation (eg, death, participant's request, loss to follow-up), whichever comes first. Tumour assessments should be scheduled using the date of the first dose of study treatment as the reference date for all time points and are <u>not</u> to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to study treatment delay is not permitted.

Bone scan, whole body MRI, or positron emission tomography (PET) scan will be carried out at baseline for all participants in Part 1 (excluding participants with neuroblastoma) and in the Part 2 Osteosarcoma Expansion Cohort within 84 days prior to the first dose of study treatment to detect bony sites of disease. Subsequent assessments are to be performed during the Treatment Period when clinically indicated. If the baseline bone scan, whole body MRI, or PET scan is positive for metastatic bone disease, a repeat assessment is required for confirmation of partial response (PR) or complete response (CR) or if clinically indicated.

The same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant.

Clinical assessment of superficial lesions should be carried out on the same date as the imaging studies or no later than 3 days thereafter and must be recorded in the participant's electronic case report form (eCRF).

Participants with neuroblastoma will undergo bone marrow assessments at Screening and, if positive at baseline, every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days)

thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation of participant from overall study participation (e.g., death, participant's request, loss to follow-up), whichever comes first.

Participants who have a PR or CR while on treatment and who discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.

Blood samples to assess niraparib PK, dostarlimab PK, and dostarlimab antidrug antibodies (ADAs) and neutralising antibodies (NAb) will be collected from all participants pre- and postdose at the time points specified in Table 3. CCI [redacted] Blood samples should be collected in order of priority as outlined in Section 8.2. Tumour samples will be collected from all participants in Part 2 and also from Part 1 participants, but only under specific circumstances such as a treatment response.

Safety assessments conducted throughout the Treatment Period include symptom-directed physical examinations, electrocardiograms (ECGs), vital signs, and clinical laboratory assessments, including complete blood count (CBC) with differential, coagulation profile, chemistry, thyroid function panel, and pregnancy (irrespective of prior medical treatment) testing. Psychological assessments will be administered as per local standard of care.

CCI [redacted]

All participants will undergo an EOT Visit conducted no more than 7 days following the decision to discontinue study treatment and a Safety Follow-up Visit 30 (+7) days after the last date of study treatment administration. Participants are expected to complete the Safety Follow-up Visit regardless of reason for study treatment discontinuation and even if they have started alternative anticancer therapy. During the long-term Follow-up Assessment Period, participants will be followed via clinic visit or telephone contact (if an in-person visit is not possible) every 90 (±14) days after the last dose of study treatment for the first year, every 180 (±14) days for the subsequent 2 years, and yearly (±14 days) for an additional 2 years (5 years total), or until the start of alternative anticancer therapy (unless there is an ongoing AE/SAE that must be followed until resolved, stabilised, or otherwise explained), or until the participant withdraws from the study overall, is lost to follow-up, or dies (whichever occurs earlier).

Collection and recording of all AEs for each participant will start on the day of informed consent/assent. Nonserious AEs will be collected until 30 days after the last dose of study treatment. Serious adverse events (SAEs) will be collected until 90 days after the last dose of study treatment (or to a minimum of 30 days after the last dose of study treatment if the participant starts alternative anticancer treatment). However, any SAEs assessed as related to study participation or related to study treatment will be collected through the

Follow-up Assessment Period. Adverse events of special interest (AESIs) are defined in Appendix 2; AESIs will be collected through the Follow-up Assessment Period as described in Section 8.3.6. Details of all pregnancies in female participants and, if indicated, female partners of male participants who receive study treatment will be collected until 180 days after the last dose of study treatment in female participants and 90 days after the last dose of study treatment for female partners of male participants. In addition, all ongoing AEs and SAEs are to be followed, regardless of start of alternative anticancer therapy, until the event is resolved, stabilised, or otherwise explained; until the participant has withdrawn consent from the study overall, is lost to follow-up (as defined in Section 7.4); or has died.

4.5. Number of Participants

Under Protocol Amendment 03, approximately 56 participants were planned to be enrolled in Part 1 of the study, including approximately 32 participants in Part 1A and approximately 24 participants in Part 1B (unless the incidence of DLTs dictated fewer participants as per the Dose Escalation Plan described in Section 4.1). See Section 9.1 for sample size considerations per cohort.

A total of 23 participants were enrolled into Part 1A Cohorts 0, 1A, and 1B. Part 1A Cohort 1B was not deemed to be safe, and, as a result, no participants were enrolled into Part 1A Cohort 2. In addition, a total of 3 participants were enrolled into Part 1B Cohort 1, for which enrolment into Part 1B Cohort 1 was prematurely stopped due to DLTs of Grade ≥3 thrombocytopenia.

Under Protocol Amendment 05, it is anticipated that, 1 to 3 cohorts (8 participants per cohort or approximately 24 participants overall) may be enrolled in Part 1B, unless the incidence of DLTs dictates fewer participants as noted in Section 4.1. Additional cohorts (including up to 8 participants per cohort) may be opened in Part 1B if needed to evaluate alternative niraparib dose levels. Lastly, up to 5 additional participants may be enrolled into Part 1B to further evaluate the youngest participant group(s) if not represented.

Numbers of participants for the Part 2 Osteosarcoma and Neuroblastoma Expansion Cohorts are discussed in the relevant protocol supplement.

4.6. Treatment Assignment

All participants in this single-arm study will receive treatment with niraparib in combination with dostarlimab.

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4.7. Dose Adjustment Criteria

4.7.1. Niraparib Dose Adjustment for Age and Weight

When a participant who is <8 years of age experiences a birthday while on study, a niraparib dose increase should be considered from the start of their next cycle i.e., Week 1 (Table 7). For example, if a 6-year-old participant receiving niraparib has a birthday and turns 7 years old, then that participant will receive a higher dose of niraparib as indicated in Table 7.

When a participant ≥8 years of age experiences a weight change while on study that moves them into a higher or lower weight dosing category in Table 7, a niraparib dose adjustment should be considered from the start of the next cycle; i.e., Week 1 of the following cycle.

If a 7-year-old participant has a birthday and turns 8-years-old while on study, then that participant will shift to the CCI [redacted]

Niraparib dose may not be adjusted in response to age increase or weight change during the first 2 cycles of therapy.

Following a dose change (increase or decrease), additional niraparib PK samples will be obtained (see Table 3, footnote x).

Following a niraparib dose increase, participants will be closely monitored (Table 3) for risk of haematological toxicities as follows:

- Part 1B and Part 2 Safety Run-in: Twice weekly CBC for the period of 2 cycles following the increase in niraparib dose.
- Part 2 Expansion Cohorts: Once weekly CBC for the period of 2 cycles following the increase in niraparib dose.

4.7.2. Dose Adjustment for Adverse Events

Adverse reactions should be managed with dose reduction, interruption of treatment, or dose discontinuation.

For dostarlimab, interruption is defined as stopping administration before completion of the infusion, including both cases in which the infusion is resumed and completed on the same day and cases in which administration is not resumed that day.

Study intervention delay is defined as withholding study intervention administration for longer than the regularly scheduled dosing interval. For dostarlimab dosing delays >12 weeks, or if AEs do not return to baseline or Grade <1 within 12 weeks (see Table 11),

dostarlimab should be permanently discontinued unless the Investigator and Medical Monitor agree there is strong evidence supporting continued treatment.

All dose reductions, treatment delays (including any missed doses) and discontinuations, and the reason for such modifications should be recorded in the eCRF.

It should be noted that required treatment discontinuation of either niraparib or dostarlimab will result in study treatment discontinuation of both treatments.

4.7.2.1. Niraparib

The recommended dose modifications for adverse reactions should be followed as listed in Table 9 and Table 10. Following a dose reduction, participants should not subsequently have dose re-escalated unless a discussion with the GSK Medical Monitor has occurred. Following 2 dose reductions, participants will not be allowed to further dose reduce, and study treatment should be discontinued. Study treatment should be discontinued for selected AEs that persist beyond 28 days, as noted below.

Table 9: Niraparib Dose Modifications for Nonhaematologic Adverse Reactions

NCI CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	• Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Participants may resume niraparib at a lower dose after discussion with the GSK Medical Monitor.[a]
NCI CTCAE Grade ≥2 adverse reaction of PRES	• Discontinue study treatment for participants.

Abbreviations: TfOS= tablet for oral suspension; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; PRES=Posterior Reversible Encephalopathy Syndrome.

CCI [redacted]

There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with PRES. PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

Table 10: Niraparib Dose Modifications for Haematologic Adverse Reactions

Weekly blood draws for CBC will be monitored until the adverse reaction resolves; after resuming niraparib, weekly blood draws for CBC will be required for an additional 4 weeks (28 days) after the adverse reaction has been resolved to the specified levels, after which monitoring at Week 1 of each cycle may resume (Table 3).	
Platelet count <100 000/µL	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL. Resume niraparib at the same or lower dose • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • If nadir platelet count was <75 000/µL, niraparib dose should be reduced. • Participants may resume niraparib at the same or a lower dose after discussion with the GSK Medical Monitor.[a.]
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • If nadir platelet count is <75,000/µL, niraparib dose should be reduced. • Participants may resume niraparib at a lower dose after discussion with the GSK Medical Monitor.[a.]
Neutrophil <1000/µL or Haemoglobin <8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1000 µL or haemoglobin returns to ≥8 g/dL. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Participants may resume niraparib at a lower dose after discussion with the GSK Medical Monitor.[a]

Haematologic adverse reaction requiring transfusion	• For participants with platelet count ≤10 000/µL, platelet transfusion should be considered. If there are other risk factors, such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Red blood cell transfusion(s) may be given at the discretion of the Investigator. • Participants may resume niraparib at a lower dose after discussion with the GSK Medical Monitor.[a]
MDS/AML	Any suspected case of MDS/AML reported while a participant is receiving treatment or being followed for post-treatment assessments must be referred for evaluation to a local haematologist to perform bone marrow aspirate and biopsy as per local standards of practice. The study site must receive a copy of the haematologist's report of aspirate/biopsy findings, which must include a classification according to the WHO, and other sample testing reports related to MDS/AML. If a diagnosis of MDS/AML is confirmed by a haematologist, the participant must permanently discontinue study treatment.

Abbreviations: TfOS= tablet for oral suspension; CBC=complete blood count.

CCI [redacted]

For clinical situations not covered by this dose modification guidance, the Investigator must contact the GSK Medical Monitor.

4.7.2.2. Dostarlimab

Given the mechanism of action of dostarlimab, it is anticipated that activation of the cellular immune system can be manifested as imAEs. An imAE is defined as an AE of any organ that is associated with study intervention exposure, is of unknown etiology, and is consistent with an immune-related mechanism. Special attention should be paid to AEs that may be suggestive of potential imAEs. Onset of imAEs can occur after the first dose, later after several doses have been administered, or several months after the last dose of immunotherapy treatment (Ramos-Casals, 2020).

Early recognition of drug-related imAEs and initiation of treatment are critical in mitigating severity and reducing the risk of complications, because the majority of imAEs are reversible with the use of steroids and other immune suppressants or therapies (Pardoll, 2012; Weber , 2012). If a drug-related imAE is suspected, the participant should return to the study site as soon as possible instead of waiting for their next scheduled visit. Participants who experience a new or worsening imAE should be contacted and/or evaluated at the study site more frequently. A thorough evaluation should be conducted to rule out neoplastic, infectious, metabolic, toxin-related, or other etiologies before diagnosing a drug-related imAE. Serological, immunological, and histological (i.e., via a biopsy) data should be considered to support the diagnosis of an immune-related toxicity. Consultation with an appropriate medical specialist should be considered when investigating a possible imAE.

For all imAEs of interest (imAEIs) listed in Table 11, dostarlimab should be held until participant is clinically and metabolically stable and AEs are resolved to Grade 1 or less. If systemic steroids are used as a part of imAEI management, total dose of daily steroids should be equal to or less than prednisone 10 mg at the time of resuming dostarlimab. All AEs are to be graded according to NCI CTCAE v5 (US Department of Health and Human Services, 2017)

Table 11 includes details on the management of dostarlimab dose delays and discontinuation for specific events. Institutional management guidelines, the SITC clinical practice guideline on immune checkpoint inhibitor-related AEs (Naidoo, 2023) and the NCCN clinical practice guideline for management of imAEs (NCCN, 2021), the ESMO clinical practice guideline for management of toxicities from immunotherapy (Haanen, 2022) and/or the ASCO guideline on management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy (Brahmer, 2021) should be consulted and used to supplement the algorithms provided below. In cases where the Investigator is directed to discontinue study intervention permanently, these instructions are mandatory; some exceptions may be permitted after consultation with the Sponsor if the dose modification/treatment guidelines in Table 11 and/or Table 12 differ from the institutional or professional society guidance. The Medical Monitor can be contacted if there are additional questions about PD-1 inhibitor-related AE management.

Table 11: Guidelines for Treatment of Immune-mediated Adverse Events

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
General instructions: This table provides guidelines for dose modifications/dose discontinuations for AEs that are suspected to be imAEs related to the ICI. Corticosteroid taper should be initiated upon AE improving to Grade ≤1 and continue to taper over at least 4 weeks. For situations where study intervention has been withheld, administration can be resumed after the AE has been reduced to Grade ≤1 and corticosteroid has been tapered. Study intervention should be permanently discontinued if the AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg/day prednisone, or equivalent, within 12 weeks. For severe and life-threatening imAEs, IV corticosteroid should be initiated first, followed by oral steroid. Other immunosuppressive treatment should be initiated if imAEs cannot be controlled by corticosteroids.				
Uveitis	Grade 2	Withhold	Urgent ophthalmology consultation. Administer treatment with ophthalmic and systemic prednisone/methylprednisolone.	Ensure adequate evaluation (e.g., urgent ophthalmology consultation).
	Grade 3 or 4	Permanently discontinue		
Diarrhoea/colitis	Grade 2-3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 to 1.	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent) followed by taper.	Monitor carefully for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). Participants with Grade ≥2 diarrhoea where colitis is suspected should consider GI consultation and an endoscopy to rule out colitis. All participants who experience diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible,
	Grade 4	Permanently discontinue		

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				fluid and electrolytes should be substituted via IV infusion.
AST/ALT elevation, increased bilirubin or hepatitis	Grade 2 with AST/ALT >3 and up to 5×ULN or total bilirubin >1.5 and up to 3×ULN	Withhold dose. Restart dosing when toxicity resolves to Grade 0 to 1. Inform GSK Medical Monitor before resuming dose.	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg methylprednisolone or equivalent) followed by taper.	Inform GSK Medical Monitor Monitor with liver function tests (consider weekly or more frequently until liver enzyme value[s] return to baseline or are stable). Ensure adequate hepatology evaluation (e.g., hepatologist consultation) See Section 7.1.1, Appendix 8 and Appendix 9 for additional details on liver event follow-up assessments.
	Grade 3 with AST / ALT >5×ULN up to 8x ULN	Discontinue See Section for liver chemistry stopping criteria and monitoring guidance, and for liver rechallenge process and criteria.	Administer corticosteroids (1 to 2 mg/kg methylprednisone or equivalent), followed by taper	Strongly recommend specialist hepatology evaluation See Section 7.1.1, Appendix 8 and Appendix 9 for liver chemistry monitoring guidance
	Grade 3 (AST or ALT >8x ULN up to 20xULN) or total bilirubin > 3xULN (up to 10xULN)	Permanently discontinue See Section 7.1.1 for liver chemistry stopping criteria and monitoring guidance	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent) followed by taper.	Inform GSK Medical Monitor See Section 7.1.1 for liver chemistry monitoring guidance. Strongly recommend specialist hepatology evaluation.
	Grade 4 (AST or ALT >20x ULN or total bilirubin >10x ULN)	Permanently discontinue See Section 7.1.1 for liver chemistry stopping criteria and monitoring guidance	Administer corticosteroids (initial dose of 2 mg/kg methylprednisolone or equivalent) followed by taper.	Inform GSK Medical Monitor See Section 7.1.1 for liver chemistry monitoring guidance.

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				Specialist hepatology evaluation is recommended.
T1DM or hyperglycaemia	Grade 3-4 hyperglycaemia or T1DM (associated with metabolic acidosis or ketonuria)	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable participants. Insulin replacement therapy is required.	Initiate insulin replacement therapy for participants with T1DM.	Monitor participants for hyperglycaemia or other signs and symptoms of diabetes. Ensure adequate evaluation (e.g., specialist consultation).
Hypophysitis	2-4	Hold until hormonal therapy results return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrence or worsening of Grade ≥2 hypophysitis after steroid taper has been completed and is on adequate hormone replacement therapy, permanently discontinue.	Administer corticosteroids and initiate HRT as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) Ensure adequate endocrine evaluation (e.g., endocrine consultation).

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Adrenal insufficiency	2-4	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to1. For recurrent or worsening Grade ≥2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue	Start treatment with corticosteroids before other HRT to avoid adrenal crisis (hydrocortisone slowly titrating doses down according to symptoms or prednisone and fludrocortisone titrating up or down based on BP, other symptoms, and laboratory results); participants with severe symptoms may require additional fluids (e.g., saline >2L).	Monitor for cortisol level (AM), comprehensive metabolic panel (Na, K, CO2, and glucose), and renin. Ensure adequate endocrine evaluation (e.g., endocrine consultation).
Hyperthyroidism	3 or 4	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1.	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders Ensure adequate evaluation (e.g., endocrine consultation).
Hypothyroidism	3 or 4	Hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0 to 1	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders. Monitor thyroid function tests. Ensure adequate evaluation (e.g., endocrine consultation). Exclude concomitant adrenal insufficiency (AM cortisol level).

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 to 1.	Administer corticosteroids (eg, 1 to 2 mg/kg/day of prednisone or equivalent) Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks (28 days).	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiological imaging and initiate corticosteroid treatment. Ensure adequate evaluation (e.g., specialist pulmonologist / respiratory opinion) Add prophylactic antibiotics for opportunistic infections (e.g., PJP).
	3-4 or recurrent Grade 2	Permanently discontinue	IV for Grade 3 to 4 (eg, 1 to 2 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks (28 days).	
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold if suspected	Treat with high potency topical steroids to affected areas. Treat with prednisone.	Ensure adequate evaluation (e.g., urgent dermatology consultation) to confirm etiology and exclude other causes.
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Administer 1 to 2 mg/kg/day IV methylprednisolone and taper steroid when dermatitis is controlled.	

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Renal failure or nephritis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 to 1.	Oral for Grade 2 (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks (28 days).	Monitor participants for signs and symptoms, including monitoring of creatinine and urine protein every 3 to 7 days. Ensure adequate evaluation (e.g., nephrology consultation, renal biopsy) to confirm etiology and exclude other causes. Consider inpatient care for Grade 3 to 4.
	3-4	Permanently discontinue.	IV for Grade 3 to 4 (1 to 2 mg/kg/day of prednisone or equivalent). Consider adding 1 of the following after 1 week of steroids: azathioprine, cyclosporine, cyclophosphamide, infliximab, mycophenolate. If persistent Grade 2 beyond 1 week, prednisone/ methylprednisolone. Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks (28 days).	
Myositis	2-3	Restart dosing when toxicity resolves to Grade 0 to 1.	Oral for Grade 2 (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) IV for Grade 3 to 4 (1 to 2 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks (28 days).	Ensure adequate evaluation.
	4	Permanently discontinue.		

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Any grade	Permanently discontinue.	Administer high-dose corticosteroids (1 g/day of IV methylprednisolone) for 3 to 5 days. If responding and stable, switch to oral prednisone taper over 6 to 12 weeks based on clinical response and improvement in cardiac biomarkers. If no improvement in 24 to 48 hours, consider adding other potent immunosuppressive agents.	Ensure adequate evaluation (e.g., urgent cardiology consultation) to confirm etiology and/or exclude other causes.
Severe neurological events (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, transverse myelitis)	Grade 2, 3, or 4	Permanently discontinue	Consider high dose corticosteroids and other therapies as needed. It is highly recommended that Investigators discuss any AEs with the Sponsor before using infliximab.	Ensure adequate evaluation (e.g., neurology consultation). Consider MRI of brain and/or spine depending on symptoms. Consider inpatient management as clinically indicated.
Encephalitis	Any grade	Permanently discontinue	Consider IV acyclovir until PCR results obtained. Trial with methylprednisolone; if severe, treatment with methylprednisolone. If positive for autoimmune encephalopathy antibody or no improvement after 7 to 14 days, consider rituximab.	Ensure adequate evaluation to confirm etiology and/or exclude other causes. Obtain specialist neurology consultation.

Toxicity	Toxicity Grade or Conditions (NCI CTCAE v5.0)	Action Taken with Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Other imAEs	Based on severity and type of reaction (Grade 2 or 3)	Withhold. Restart dosing when toxicity resolves to Grade 0 or 1.	Based on severity of AE, administer corticosteroids. When controlled, taper steroid.	Ensure adequate evaluation (including specialist consultation) to confirm etiology and exclude other causes.
	Grade 4 or recurrent Grade 3	Permanently discontinue.		
Recurrence of imAE in this table after resolution to Grade ≤1	Grade 1 or 2	Withhold (except for pneumonitis, see above).	Based on severity of AEs, administer appropriate treatment until symptoms improve to Grade ≤2.	Ensure adequate evaluation (e.g. specialist opinion).
	3-4	Permanently discontinue.		
Hemophagocytic lymphohistiocytosis (HLH)	Suspected HLH	Withhold	Obtain specialist opinion for diagnosis and management.	Obtain specialist opinion for monitoring and follow-up.
	Confirmed HLH	Permanently discontinue	Obtain specialist opinion for management.	

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; HRT=hormone replacement therapy; ICI=immune checkpoint inhibitor; imAE=immune-mediated adverse event; imAEI=immune-mediated adverse event of interest; PCR=polymerase chain reaction; T1DM=type 1 diabetes mellitus; ULN=upper limit of normal; SJS=Stevens-Johnson syndrome; TEN= toxic epidermal necrolysis; DRESS=Drug Rash with Eosinophilia and Systemic Symptoms.

Participants receiving IV study treatment may develop signs and symptoms of an infusion reaction during or shortly after drug infusion. These reactions generally resolve completely within 24 hours of completion of infusion. Table 12 shows treatment guidelines for participants who experience infusion-related reactions associated with administration of study treatment, including actions to be taken with the study treatment, if necessary.

Table 12: Infusion Reaction Treatment Guidelines

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; treatment not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include, but is not limited to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be withheld until symptoms resolve, and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration**.	Participant may be premedicated 1.5 hours (± 30 minutes) prior to infusion of dostarlimab with the following: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4**: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include, but is not limited to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. Hospitalisation may be indicated. **Participant is permanently discontinued from further study treatment administration.**	No subsequent dosing.

Abbreviations: IV=intravenous; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID=nonsteroidal anti-inflammatory drug; PO=orally.

Note: Appropriate resuscitation equipment should be available in the room and a physician is readily available during the period of study treatment administration.

4.8. End of Study Definition

The end of the study is defined as the date of completion of the last visit of the last participant in the study or the date of completion of the last scheduled procedure shown in the applicable SoA for the last participant in any part of the study globally.

A participant is considered to have completed the study if the participant has completed all study assessments, including the last scheduled procedure shown in Table 3 for Part 1 and in the SoAs specific to the cohorts provided in the supplements.

4.9. Study Conduct

4.9.1. Procedures by Visit

Standard of care tests/procedures, including laboratory assessments, ECG, physical examination, vital signs, height, weight, and performance status, performed before the enrolment into the study can be used as part of the screening assessments as long as the tests/procedures are performed within this visit window indicated in Table 3. Local laboratory assessments (chemistry, coagulation, and haematology) must be performed, and results reviewed within 7 days prior to administration of the first dose of study treatment, as indicated in Table 3. Tumour assessment (CT or MRI), MIBG-SPECT/CT or FDG-PET/CT scan (participants with neuroblastoma only), and bone scan, whole body MRI, or PET scan (Part 1 [excluding participants with neuroblastoma] and Part 2 Osteosarcoma Expansion Cohort) obtained per the standard of care prior to the first dose of study treatment (within 28 days for CT or MRI, 42 days for MIBG-SPECT/CT or FDG-PET/CT, and 84 days for bone scan, whole body MRI, or PET scan) do not need to be repeated and are acceptable to use as baseline evaluations if the conditions presented in Section 8.1.2.1 are met. Source documents must clearly identify the standard of care tests/procedures that are used for Screening, and the results of these tests/procedures must be entered in the eCRF. Table 3 details which procedures are performed at each visit.

4.9.2. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic

Due to the significant challenges that currently face the healthcare system and participants due to Coronavirus Disease 2019 (COVID-19), as well as the potential for enduring or additional quarantine measures, the following guidance is being provided in this protocol. In the spirit of global diversity in the COVID-19 pandemic and its impact on healthcare in each individual country as well as the recently issued guidance by several regulatory authorities, the autonomy of each investigative site to assess the benefit/risk for their participants participating in clinical studies should be maintained.

Prior to utilisation of any of the measures outlined in this section, discussion and approval must be obtained from Sponsor/contract research organisation.

It is expected that sites participating in clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the SoA (Table 3). The use of local laboratories and local radiology centres to reduce the need for a participant to come into the clinic are

supported, if deemed necessary for the well-being of the participant. These local facilities should be added to regulatory documents, as required.

Additionally, regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring programs to maintain oversight of clinical sites. Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor/contract research organisation.

General rules for participants with limited possibility to travel are as follows:

- If possible, replace in-person visits with phone contact or alternative location for assessment (eg, local laboratories and imaging centres).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Participant Inclusion Criteria

Participant will be eligible for Part 1 of the study if all of the following criteria are met:

CCI

[redacted]

2. Participant is child or adolescent ≥6 months to <18 years old at the time of informed consent/assent. If a participant is enrolled under Protocol Amendment 05, the participant must be ≥6 months to <8 years old at the time of informed consent/assent.
3. Participant with disease other than neuroblastoma has radiologically measurable disease at screening that can be tracked as RECIST v1.1 target lesion(s) .

   Participant with neuroblastoma has measurable/evaluable target and/or non-target disease by International Neuroblastoma Response Criteria (INRC) at screening. Neuroblastoma participants with recurrent/relapsed bone metastasis that is MIBG-positive (or FDG-positive, for MIBG-nonavid tumours) as only site of disease are eligible.

CCI

[redacted]

5. Performance status must be ≥60% on the Karnofsky scale for participants >16 years of age and ≥60% on the Lansky scale for participants ≤16 years of age.

   Note: Neurologic deficits in participants with brain metastases must have been stable for at least 7 days prior to study enrolment. Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status.

6. Participant has adequate organ function, defined as follows:

   Note: The participant must not have received blood transfusion, growth factors, or platelet stimulating agents in the 14 days prior to providing a sample for haematologic analysis nor erythropoietin in the prior 6 weeks.

   a. absolute neutrophil count (ANC) ≥1000/µL
   b. platelets ≥100 000/µL
   c. haemoglobin ≥8 g/dL or ≥5.0 mmol/L
   d. serum creatinine≤1.5×upper limit of normal (ULN) for age or calculated creatinine clearance or radioisotope glomerular filtration rate ≥60 mL/min/1.73m^2
   e. total bilirubin ≤1.5×ULN or direct bilirubin ≤1×ULN
   f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN unless liver metastases are present, in which case AST and ALT must be ≤5×ULN
   g. international normalised ratio or prothrombin time (PT) ≤1.5×ULN unless the participant is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
   h. activated PTT ≤1.5×ULN unless the participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding and at least one of the following conditions applies:

   a. Is not a woman of childbearing potential (WOCBP).

   or

   b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3, from the Screening Visit through at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
   c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours prior to the first dose of study treatment and irrespective of prior medical treatment.

   Additional requirements for pregnancy testing during and after the Treatment Period are located in Section 8.2.9.

The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. A male participant of reproductive potential is eligible to participate if he agrees to the following starting with the first dose of study treatment through at least 90 days (a spermatogenesis cycle) after the last dose of study treatment:
   a. refrain from donating sperm

   plus, either:

   b. be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

   or

   c. must agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant
9. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.

Inclusion criteria for Part 2 of the study are described in each cohort-specific supplement.

5.2. Participant Exclusion Criteria

Participant will not be eligible for study entry if any of the following criteria are met:

1. Participation presents unacceptable risk to the prospective participant based on the Investigator's judgment.
2. Participant has known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.
3. Participant has a known history of myelodysplastic syndrome (MDS) or AML.
4. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying antirheumatic drugs, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
5. Participant has known active CNS metastases, carcinomatous meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are clinically stable and have no evidence of new, enlarging, or progressing brain metastases (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks (28 days) prior to the first dose of study treatment. In addition, the participant must have not been using steroids for at least 7 days prior to

the first dose of study treatment. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.

6. Participant had a known (second primary) additional malignancy that progressed or required active treatment within the last 2 years.
7. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining assent/consent).
8. Participant has a condition (such as transfusion-dependent anaemia or thrombocytopenia), requirement for therapy, or laboratory abnormality that might confound the study results or interfere with the participant's participation for the full duration of the study treatment.
9. Participant is pregnant, breastfeeding, or expecting to conceive within the projected duration of the study, starting with the Screening Visit through 180 days after the last dose of study treatment.

   No data are available regarding the presence of dostarlimab or niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from dostarlimab and/or niraparib, female participants should not breastfeed during treatment with dostarlimab and/or niraparib and for at least 4 months after the last dose of dostarlimab or at least 30 days after the last dose of niraparib, whichever is longer.
10. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
11. Participant has a known history of HIV (type 1 or 2 antibodies).
12. Participant has documented presence of HbsAg and/or HBcAb at Screening or within 3 months prior to first dose of study intervention. Participants with a negative HbsAg and positive HbcAb result are eligible only if HBV DNA is negative (Appendix 12)
13. Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.
14. Participant has had any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer treatment and that persisted >4 weeks (28 days).
15. Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic anticancer therapy-induced AEs. Note: Participants with alopecia, hearing

impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤ 2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.

16. Participant had toxicity related to prior immunotherapy that led to treatment discontinuation.
17. Participant had treatment with systemic anticancer therapy (investigational agent or device, or approved chemotherapy, targeted therapy, immunotherapy, or other systemic therapy) within 3 weeks or 5 half-lives, whichever is shorter, prior to the first dose of study treatment; radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment; or any radiation therapy within 1 week prior to the first dose of study treatment.
18. Participant has not recovered adequately from AEs or complications from any major surgery prior to starting study treatment.
19. Participant has received a live vaccine within 30 days of planned start of study treatment.
20. Participant has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, and history of cerebrovascular accident) within 6 months of enrolment.
21. Participant has heart rate-corrected QT interval prolongation at screening >450 msec or >480 msec for participants with bundle branch block.

    Notes:

    - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine read or manually over read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual participant must be determined prior to initiation of the study and used consistently for eligibility and study assessments.
22. Participant has received a solid organ transplant.
23. Participant has a documented presence of HCV antibody at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, if a confirmatory HCV RNA test is negative and the participant otherwise meets entry criteria.
24. Participant has a documented presence of HCV RNA at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well.

Exclusion criteria for Part 2 of the study are described in each cohort-specific supplement.

5.3. Lifestyle Considerations

Cases of photosensitivity have been reported for patients on niraparib treatment. Participants must be informed on measures to decrease exposure to ultraviolet light, such as minimising time in direct sunlight unless wearing hats and long-sleeves and application of sun protection creams.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, any protocol deviations, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

6. STUDY TREATMENTS(S) AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

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The dosing regimens for niraparib in Part 1B and Part 2 under Protocol Amendment 05 are shown in Table 7 in Section 2.6.3.1.

Details for suspension and administration of the TfOS are included in the Pharmacy Manual.

Dostarlimab is an IgG4-κ humanised mAb that binds with high affinity to PD-1 and will be supplied for all study parts as a solution for intravenous (IV) infusion in single-use 10-mL vials containing 500 mg (50 mg/mL).

Details about the investigational products are provided in Table 13.

Table 13: Investigational Products

Intervention name	CCI [redacted]		
Dosage formulation			
Type	Drug	Drug	Biologic
Unit dose strength(s)	CCI [redacted]		
CCI [redacted]			
Use	IMP	IMP	IMP
Authorised AxMP/ Unauthorised AxMP	Not applicable	Not applicable	Not applicable
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Physical description (Packaging and Labelling; see Section 6.2.1)	CCI [redacted]		
Dosage level(s)	See Section 2.6.3.1, Table 7	See Section 2.6.3.1, Table 7	See Section 2.6.3.2
Manufacturer	WuXi STA (WuXi), China (DS, DP) Dishman, India (DS) Corden, Colorado, US (DS) Mayne Pharma, Raleigh, North Carolina, US (DP) Siegfried, Switzerland (DS)	WuXi STA (WuXi), China (DS, DP) Corden, Colorado, US (DS) Dishman, India (DS) Siegfried, Switzerland (DS)	WuXi Biologics (WuXi), Wuxi, China (DS) Ajinomoto Althea (Aji), San Diego, California, US (DP)

Abbreviations: AxMP = auxiliary medicinal product; DP=drug product; DS=drug substance; IMP = investigational medicinal product; IV=intravenous; Non-IMP = non-investigational medicinal product; CCI [redacted]; US=United States.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Treatment Packaging and Labelling

Previously, niraparib CCI [redacted] were used by participants in all cohorts of Part 1A and niraparib CCI [redacted] was used by participants in Part 1B Cohort 1 under Protocol Amendment 03. TfOS will be used by participants under Protocol Amendment 05. Niraparib will be packed in high-density polyethylene bottles with child-resistant closures. CCI [redacted]

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-participant-specific.

6.2.2. Study Treatment Storage

All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labelling. Until dispensed or administered to the participants, the study treatments will be stored in a securely locked area that is accessible only to authorised personnel.

6.2.3. Administration

Details on the administration of the study treatments can be found in the Pharmacy Manual. A summary is provided below.

6.2.3.1. Niraparib

Oral niraparib will be dispensed to participants on Day 1 of every 21 -day cycle beginning with Cycle 1 of the Treatment Period until the end of the Treatment Period, PD, unacceptable toxicity, withdrawal of consent/assent, Investigator's decision to withdraw, or death. On day 1 of each cycle, niraparib should be administered while at the site and after completion of the dostarlimab infusion.

Participants will be instructed to take their niraparib dose once daily at approximately the same time each day. Niraparib will be self-administered or administered to the child by the parent/caregiver. CCI [redacted] The consumption of water and food (i.e., light meal) with niraparib is permissible. If a participant vomits or misses a dose of niraparib, a replacement dose should not be taken.

CCI [redacted]

CCI [redacted]

6.2.3.2. Dostarlimab

Dostarlimab infusion will be administered before the niraparib dose at the study site on Day 1 of each 21-day treatment cycle (Q3W). Dostarlimab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons. If dostarlimab is administered on Day 1 of the cycle, it will be administered after all procedures and assessments have been completed, unless otherwise indicated.

Participant dosing with dostarlimab is based on assigned cohort and participant weight at Week 1 of each treatment cycle, CCI [redacted]. Actual dostarlimab dosing within ±10% of the calculated weight-based dose is acceptable.

Dostarlimab will be administered through a 30-minute infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, however, a window between -5 minutes and +15 minutes is permitted, in the absence of any clinically significant infusion-related reaction that would necessitate interruption and/or increased infusion interval. Participants should remain under observation at the study site post-study treatment infusion per the judgement of the Investigator or as per institutional guidelines to monitor for potential infusion reactions or other AEs.

6.2.4. Study Treatment Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

Details of maintaining drug accountability, including information on the accountability log, will be provided in the Pharmacy Manual.

The Study Monitor will assume the responsibility to reconcile the niraparib and dostarlimab study treatment accountability logs. The pharmacist will dispense niraparib and dostarlimab study treatment for each participant according to the protocol and Pharmacy Manual.

6.2.5. Study Treatment Handling and Disposal

At the end of study, when all participants have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study treatment according to local regulations. If a site does not have the capability for on-site destruction, the Sponsor will provide a return for destruction service through a third party. Both the unused and expired study treatment must be destroyed, upon authorisation of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

The medication provided for this study is to be used only as indicated in this protocol and only for the participants entered in this study.

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment.
- All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.
- Precaution will be taken to avoid direct contact with the study intervention. An MSDS describing occupational hazards and recommended handling precautions will be provided to the Investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomised, open-label study.

6.4. Study Treatment Compliance

When participants are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

A dosing diary was used during the first 2 treatment cycles for participants in Part 1A in order to monitor treatment compliance during the DLT observation phase for the [redacted]

Under Protocol Amendment 05, all participants treated with the niraparib [redacted] will be expected to record all [redacted] use in the dosing diary to permit ongoing monitoring of dosing compliance.

6.5. Dose Modification

Specific dose modifications are included in Section 4.7**.** Any required dose modifications should be captured in the eCRF.

6.6. Treatment of Overdose

Young children are much less likely to report an overdose. The Investigator should warn parents/caregivers to store the study treatment out of reach of children.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until the investigational product can no longer be detected systemically.
- Document the quantity of the excess dose as well as the duration of the overdosing in the case report form (CRF).

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.7. Continued Access to Study Intervention After the End of the Study

Given that the end of study overall occurs when the last participant completes their last visit or last procedure, there will be no participants on the study in any capacity at the time that end of study occurs and, therefore, no need to provide study treatment to any ongoing participant.

6.8. Concomitant Therapy

Any medication that the participant is receiving, including herbal and other non-traditional remedies, at the time of screening or during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Rescue Medications

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including but not limited to the items outlined below. Prophylactic cytokines (eg, G-CSF) should be administered according to current ASCO guidelines [Smith, 2015] (except in Cycle 1 per Section 6.8.2).

Note: it may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.8.2. Prohibited Medications

Known prior medications that exclude participants from participating in the study are described in the exclusion criteria (Section 5.2).

Participants are prohibited from receiving the following therapies during the Screening and Treatment periods of this study:

- Systemic anticancer or biological therapy.
- Immunotherapy not specified in this protocol.
- Local interventions (such as radiotherapy) to RECIST v1.1/INRC target lesions prior to PD (unless discussed with and approved by GSK's Medical Monitor).
- Investigational agents other than niraparib and dostarlimab.
- Prophylactic cytokines (e.g., G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to local guidelines.
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected imAEs. (Note: Use of inhaled steroids, local injection of steroids, topical steroids, and steroid eye drops are allowed.) If medically deemed necessary (e.g., acute asthma or chronic obstructive pulmonary disease exacerbation, prophylaxis for IV contrast if indicated), Investigators are allowed to use their judgment to treat participants with systemic steroids. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of dostarlimab.

The combination of niraparib with vaccines or immunosuppressant agents has not been studied.

The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Concomitant administration of dostarlimab and live vaccines are prohibited during the study and for a period of at least 180 days after the last dose.

No other anticancer treatment is permitted during the course of the study treatment for any participant. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics, as long as no evidence of PD is present.

The niraparib safety profile includes risk for thrombocytopenia; therefore, participants should be advised to use caution when taking anticoagulants (e.g., warfarin) and antiplatelet drugs (e.g., aspirin).

No clinical drug interaction studies have been performed with niraparib. In vitro data and physiologically based PK (PBPK) modeling indicated no clinically relevant inhibition or induction of drug-metabolizing cytochrome P450 enzymes and no clinically relevant inhibition of most efflux transporters or uptake transporters.

Niraparib is an inhibitor of MATE-1 and -2K with IC_{50} of 0.18 μM and ≤0.14 μM, respectively. Simulations using PBPK modeling indicate an expected >2-fold increase in exposure of metformin when administered with niraparib at 200 mg or 300 mg daily. Close monitoring of glycemia is recommended when starting or stopping niraparib in patients receiving metformin. A dose adjustment of metformin may be necessary.

Physicians should follow the current versions of the niraparib IB and the dostarlimab IB for information on the general management of the participants participating in the study.

6.8.3. Other Study Restrictions

Participants who are blood donors should not donate blood during the study and for 90 days after the last dose of study treatment.

Participants should maintain a normal diet, unless modifications are required to manage an AE such as diarrhoea, nausea, or vomiting.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Participants may be discontinued from study treatment at any time. Participants who discontinue from study treatment will not be replaced, unless deemed unevaluable for assessment of DLT as defined in Section 4.3.

Participants who discontinue study treatment will attend the EOT Visit no more than 7 days following the decision to discontinue study treatment and a Safety Follow-up Visit 30 (+7) days after the last dose of study treatment. Participants are expected to complete the Safety Follow-up Visit regardless of reason for study treatment discontinuation and even if they have started subsequent anticancer therapy. Initiation of alternative anticancer therapy does not require withdrawal from the study overall. During the long-term Follow-up Assessment Period, participants will be followed via clinic visit or telephone contact (if an in-person visit is not possible) every 90 (±14) days after the last dose of study treatment for the first year, every 180 (±14) days for the subsequent 2 years, and yearly (±14 days) for an additional 2 years (5 years total), until the start of alternative anticancer therapy (unless there is an ongoing AE/SAE that must be followed until resolved, stabilised, or otherwise explained), or until discontinuation of the participant from the study overall, is lost to follow-up (as defined in Section 7.4), or dies (whichever occurs earlier).

Specific reasons for discontinuing treatment include the following, in addition to those indicated in Section 4.7. Discontinuation of study treatment does not require discontinuation of participation in the study overall.

- AE, which may include DLTs and recurrence of AEs upon rechallenge with study treatment.
- MDS/AML (as confirmed by a haematologist)
- Second primary malignancies other than MDS/AML may require discontinuation to be assessed by the treating physician in agreement with the Sponsor.
- Hypertensive crisis/PRES
- if the participant is required to discontinue either niraparib or dostarlimab, then discontinuation of all study treatments is mandated.
- if there is risk to the participant as judged by the Investigator, Sponsor, or both.
- if the participant has had severe noncompliance with protocol as judged by the Investigator, Sponsor, or both.
- if the participant becomes pregnant
- if the participant withdraws assent and/or the parent(s)/guardian(s) withdraw consent
- if the participant is lost to follow-up
- if the participant dies

- if the participant has PD according to RECIST v1.1 criteria or INRC (participants with neuroblastoma only) or symptomatic deterioration necessitating a change in therapy in the opinion of the Investigator (see below)
- initiation of new alternative anticancer therapy

There is accumulating evidence indicating clinical benefit in a subset of patients treated with immunotherapy despite evidence of PD (Nishino, 2015). Therefore, participants with radiologic evidence of PD who are clinically stable may continue study treatment at the Investigator's discretion, after discussion with the participant's legally acceptable representative, parent(s), and/or legal guardian and after consultation with the Sponsor, while awaiting confirmatory tumour imaging. Clinical stability is defined by the following criteria:

- absence of signs and symptoms indicating clinically significant PD (including worsening of laboratory values)
- absence of rapid PD
- no decline in performance status
- no progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent medical intervention.

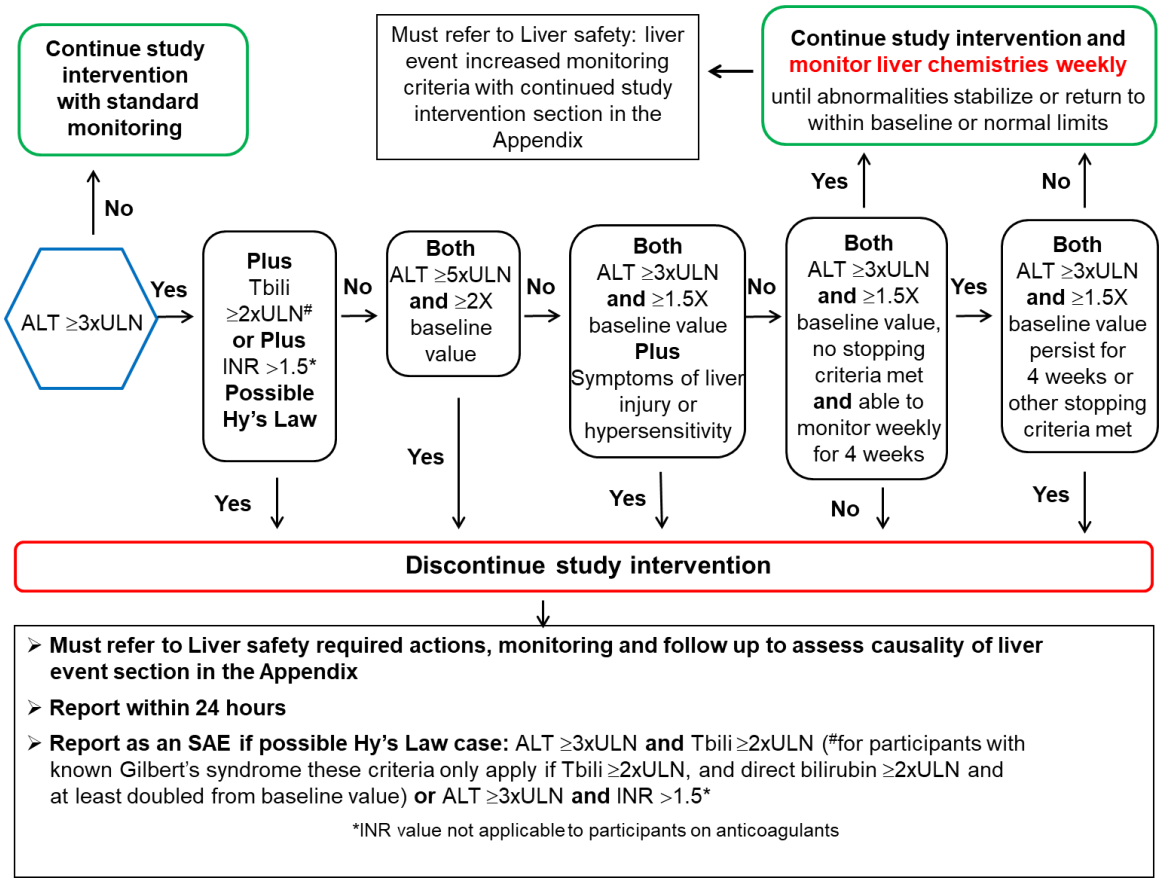
Repeat imaging should be performed at 4 to 6 weeks from the initial assessment of PD. If repeat imaging assessment following RECIST v1.1 or INRC (participants with neuroblastoma only), shows stable disease (SD), PR, or CR, participants can continue study treatment at the Investigator's discretion and efforts should be made to return to the imaging visit schedule defined in the SoA. In the event that PD is confirmed (e.g., second overall response of PD per RECIST v1.1 or INRC), participants should discontinue study treatment.

Participants who discontinue from all study treatments without documented PD will continue to receive follow-up assessments and tumour imaging as part of the study unless they are discontinued from the study overall.

7.1.1. Liver Chemistry Stopping Criteria

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met.

Figure 6: Phase I/II Liver Chemistry Stopping and Monitoring Event Algorithm



Refer to Appendix 8 for Required Liver Safety Actions, Monitoring and Follow-up to Assess Causality of Liver Events and Appendix 9 for Liver Safety Drug Restart or Rechallenge Guidelines.

7.1.2. QTc Stopping Criteria

A participant who meets the bulleted criterion will be withdrawn from study treatment:

- QTc >500 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed in Table 14:

Table 14: Bundle Branch Block QTc Discontinuation Criteria

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

7.2. Withdrawal of Consent

If consent is withdrawn (i.e., a participant withdrew assent and/or parent(s)/guardian(s) withdrew consent), then the participant/participant's parent/guardian(s) will no longer be contacted by the Investigator. However, any information that can subsequently be found in the public domain may be used by the Investigator or a third party acting on behalf of the Investigator.

7.3. Participant Discontinuation/Withdrawal from the Clinical Study

- A participant may withdraw from the study at any time at their own request and/or at the request of their parent/guardian for any reason (or without providing any reason); reasons may include withdrawal of consent/assent, death, lost to follow-up, study terminated by the Sponsor.
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study treatment and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested for further research, and the Investigator must document this in the site study records.
- Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.
- Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons.

Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved.

7.4. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Timings for all procedures and assessments are provided in the SoA (Table 3). Sites are to consult with the GSK Medical Monitor for any procedure that is anticipated to be completed outside the required time window.

8.1. Assessment of Efficacy

8.1.1. Primary Efficacy Endpoint

Not applicable.

8.1.2. Secondary Efficacy Endpoints

Efficacy of the combination of niraparib and dostarlimab is part of the secondary objectives of the study. Secondary efficacy endpoints include ORR and DOR as assessed by the Investigator per RECIST v1.1 (Eisenhauer, 2009; Schwartz, 2016) or INRC (Park, 2017) (for participants with neuroblastoma only).

8.1.2.1. Radiologic Assessments

All participants will undergo serial radiologic assessments to assess tumour response in accordance with Table 3 and Table 4.

Timing and Considerations for Radiologic Assessments

Participants must have a baseline tumour assessment (CT or MRI*) of the chest, abdomen, pelvis, and any additional sites** as clinically indicated within 28 days prior to the first dose of study treatment. Participants with neuroblastoma must also have a baseline tumour assessment via MIBG-SPECT/CT or FDG-PET/CT within 42 days prior to the first dose of study treatment.

*CT scans should be performed with contrast agents unless contraindicated for medical reasons. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such a case, CT will be performed without contrast to evaluate the lung parenchyma. If MRI is used to follow-up bone lesion(s), it must be performed prior to any treatment that may affect bone marrow cellularity (e.g., G-CSF). PET/CT may be used according to RECIST v1.1 or INRC (participants with neuroblastoma only) guidelines with full-dose diagnostic CT and as clinically indicated.

**A baseline brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT) is required for participants with previously treated brain metastases. (Participants with previously treated brain metastases may participate under the conditions detailed in exclusion criterion 5 in this master protocol and in the exclusion criteria of each cohort-specific supplement for Part 2).

Tumour assessments by CT or MRI of sites involved by disease at baseline and of any additional sites as clinically indicated will be done postbaseline, as will MIBG-SPECT/CT or FDG-PET/CT tumour assessments (participants with neuroblastoma only). Tumour assessments should be conducted every 9 weeks (every 63 [±7] days) from the

start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation of participant from overall study participation (eg, death, participant's request, loss to follow-up), whichever comes first. Tumour assessments should be scheduled using the date of the first dose of study treatment as the reference date for all time points and are not to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to study treatment delay is not permitted. Participants who have already demonstrated documented PD as per RECIST v1.1 or INRC (participants with neuroblastoma only) do not need to have tumour assessments repeated at the EOT Visit or during the Post-Treatment FUP. Participants who do not have documented PD at time of study treatment discontinuation will continue to undergo tumour assessments on their original schedule (i.e., every 9 weeks [every 63 ±7 days] from the start of study treatment for the first 12 months and then every 12 weeks [every 84 ±7 days] thereafter, until documented PD, start of alternative anticancer treatment, or discontinuation from overall study participation [e.g., death, participant's request, or participant is lost to follow-up], whichever comes first).

Bone scan, whole body MRI, or PET scan will be carried out at baseline for all participants in Part 1 (excluding participants with neuroblastoma) and in the Part 2 Osteosarcoma Expansion Cohort within 84 days prior to the first dose of study treatment in order to detect bony sites of disease. Subsequent assessments are to be performed during the Treatment Period when clinically indicated (i.e., participant describes new or worsening bone pain, or other signs or symptoms of new/progressing bone metastases are present). If the baseline bone scan, whole body MRI, or PET scan is positive for metastatic bone disease, a repeat assessment is required for confirmation of PR or CR.

Participants who have a PR or CR while on treatment and who discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.

Radiologic assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations if all of the following conditions are met: (1) the CT or MRI tumour assessments were obtained within 28 days prior to the first dose of study treatment/the MIBG-SPECT/CT or FDG-PET/CT tumour assessments were obtained within 42 days prior to the first dose of study treatment (participants with neuroblastoma only)/the bone scan, whole body MRI, or PET tumour assessments were obtained within 84 days prior to the first dose of study treatment (Part 1 [excluding participants with neuroblastoma] and in the Part 2 Osteosarcoma Expansion Cohort), (2) the assessments were performed using the method requirements outlined in RECIST v1.1 or INRC (participants with neuroblastoma only), (3) the same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant, and (4) appropriate documentation indicating that these radiologic tumour assessments were performed as standard of care is available in the participant's source notes.

Clinical assessment of superficial lesions should be carried out on the same date as the imaging studies or no later than 3 days thereafter and must be recorded in the participant's eCRF.

Participant scan data are not routinely collected in this study. However, such data may be requested under special circumstances, such as during investigation of a significant safety event.

8.1.2.1.1. Evaluation of Tumour Response

Evaluation of tumour response will be according to RECIST v.1.1 guidelines or INRC (for participants with neuroblastoma only).

8.1.2.2. Bone Marrow Assessments

Participants with neuroblastoma will undergo bone marrow assessment in accordance with Table 3. If positive at baseline, bone marrow samples will be obtained every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, loss to follow-up), whichever comes first.

Bone marrow assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations if the assessments were obtained within 28 days prior to the first dose of study treatment.

8.1.2.3. ORR Based on Investigator Assessment

ORR based on Investigator assessment is defined as the proportion of participants with a best overall response (BOR) of confirmed CR or PR as determined by the Investigator using RECIST v1.1 or INRC (for participants with neuroblastoma only).

8.1.2.4. Duration of Response

DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 or INRC (for participants with neuroblastoma only) based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmed CR or PR. Participants who do not experience PD or die after they have had a response are censored at the date of their last tumour assessment.

CCI

8.2. Assessment of Safety

Planned time points for all safety assessments are provided in the SoA.

At some timepoints, the protocol may specify that blood samples for clinical care (i.e., clinical chemistry, haematology, pregnancy) and for study-related research (PK, exploratory biomarkers) be obtained during a single study visit. In the event of concern for excessive blood volume withdrawal, sample collection should be prioritised as follows:

1. clinical care
2. niraparib PK
3. dostarlimab PK, ADA, and NAb

CCI [redacted]

8.2.1. Safety Parameters

Safety parameters will include the incidence of treatment-emergent adverse events (TEAEs), SAEs, study treatment-related SAEs, imAEs and AESIs. Clinical laboratory assessments (haematology, chemistry, coagulation, thyroid function), urinalysis (if obtained), vital sign measurements, performance status, ECG parameters, observations during physical examination, and use of concomitant medications will be collected.

All safety parameters will be performed in accordance with Table 3.

8.2.2. Demographic/Medical History

Demographic and baseline characteristics consist of those variables that are assessed at screening/baseline. Participant demographics consist of gestational age (for participants ≤2years of age at screening), race, ethnicity, and sex.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.2.3. Disease History

For disease history, the following will be documented:

- date of initial diagnosis
- tumour type
- stage at time of initial diagnosis
- last relapse date

8.2.4. Medical and Surgical History

Major medical and surgical history (including prior anticancer treatments and surgeries for the disease under study) will be collected. Details of any other prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the participant or the participant's legally authorised representative (LAR) or by reviewing the participant's medical records.

8.2.5. Electrocardiogram

Standard 12-lead ECGs will be performed in accordance with Table 3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG should be repeated at Cycle 3 Week 1 and EOT, as well as during the Treatment or Follow-up Periods if clinically indicated.

CCI

8.2.7. Physical Examination

Physical examinations and symptom-directed physical examinations will be performed in accordance with Table 3. Any physical examination abnormalities assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the finding should be recorded and reported according to the SAE reporting process (see Appendix 2).

8.2.8. Vital Signs, Height, and Weight

Vital signs, height, and weight will be measured in accordance with Table 3. Vital signs will include temperature, blood pressure, heart rate, and respiratory rate. All vital signs will be taken before, every 15 to 30 minutes during, and at the end of every dostarlimab infusion. Throughout the Treatment Period, all vital signs will be monitored at Week 1 of each cycle even if dostarlimab is not administered. In addition, for the first 8 weeks of the Treatment Period (up to and including Cycle 3 Week 2), all vital signs will be monitored at Week 2 and Week 3 of each cycle. Height and weight will be measured at screening, Day 1 of each cycle, EOT, Safety Follow-up, and during the Follow-up Assessment Period.

Any vital sign abnormalities assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met, the finding should be recorded and reported according to the SAE reporting process (see Appendix 2).

8.2.9. Pregnancy Testing

Niraparib is known to have properties that require the participant to use contraception and may have adverse effects on a foetus in utero. It is not known if dostarlimab may have adverse effects on a foetus in utero in humans. However, murine models of allogeneic pregnancy showed that blockade of PD-L1 signalling can eliminate foetomaternal tolerance and cause spontaneous abortion as indicated by increase in embryo resorption and a reduction in litter size (D'Addio, 2011). Human IgG4 antibodies are known to cross the placental barrier. Dostarlimab, being an IgG4, has the potential to be transmitted from

the mother to the developing foetus. Therefore, there is a risk associated with the administration of dostarlimab to WOCBP.

If a participant is of childbearing potential, a urine or serum pregnancy test will be performed in accordance with Table 3 irrespective of prior medical treatment. The results from these tests must be available and negative before study treatment is administered. Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected.

Any pregnancies that occur in female participants within 180 days after the last dose of study treatment or in partners of male participants within 90 days after the last dose of study treatment are to be reported as described in Section 8.3.5.

8.2.10. Performance Status

Performance status will be assessed using the Karnofsky scale for participants >16 years of age and the Lansky scale for participants ≤16 years of age in accordance with Table 3.

8.2.11. Psychological Assessments

Psychological assessments will be performed in accordance with Table 3 and as per local standard of care.

8.2.12. Laboratory Assessments

Laboratory variables will be determined in accordance with Table 3. The list of clinical laboratory tests to be performed is provided in Table 15. Parameters must be measured within 7 days prior to Cycle 1 Day 1 to confirm eligibility. These tests will be performed by the local laboratory at the clinical site. If Cycle 1 Day 1 is no more than 7 days after sample collection for Screening, these samples do not need to be collected again for Cycle 1 Day 1, unless clinically warranted. (Note: Baseline platelet count of 100 000/µL is considered acceptable for use in this trial considering age-related differences in platelet counts and impact of prior therapies.)

Any abnormal laboratory value assessed as clinically significant should be recorded as an AE. If SAE criteria are met or if the laboratory abnormality is an AESI, the event should be recorded and reported according to the SAE reporting process (see Appendix 2).

Haematologic, blood chemistry, and coagulation factor testing may occur more frequently than is specified in Table 3, according to local standard of care, if medically indicated per Investigator judgment, or if the event meets the criteria for study treatment dose modification (see Section 4.7). Additional tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the participant's study file, and the results must be entered into the eCRF.

Any suspected case of MDS/AML reported while a participant is receiving treatment or being followed for post-treatment assessments must be referred for evaluation to a local haematologist to perform bone marrow aspirate and biopsy as per local standards of practice. The study site must receive a copy of the haematologist's report of aspirate/biopsy findings, which must include a classification according to WHO, and

other sample testing reports related to MDS/AML. Report data will be entered in the appropriate eCRF pages, and the site must keep a copy of all reports with the participant's study file. If a diagnosis of MDS/AML is confirmed by a haematologist, the participant must permanently discontinue study treatment.

Any suspected case of second primary malignancy (new malignancies other than MDS/AML) reported while a participant is receiving treatment or followed for post-treatment assessments must be investigated, including obtaining and documenting a histological diagnosis. Testing completed as part of standard of care is sufficient as long as the methods are deemed acceptable after consultation with the GSK Medical Monitor.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

Table 15: Safety Laboratory Assessments

Laboratory Assessments	**Parameters**	
Haematology	CBC: • haemoglobin • platelet count • white blood cell count • differential white blood cell count*	Coagulation factors: • international normalised ratio • activated PTT
Blood Chemistry	Sodium, potassium, chloride, calcium, magnesium, glucose, total bilirubin, ALP, AST, ALT, total protein, albumin, creatinine, urea or blood urea nitrogen, amylase, thyroid function (thyroid-stimulating hormone [TSH], triiodothyronine [T3] or free triiodothyronine [FT3], and free thyroxine [FT4] or equivalent).	

* Either absolute counts or percentages may be recorded for differential values.

8.2.13. Drug Screen

Not applicable.

8.2.14. Viral Disease Testing

CCI [redacted] or in response to any future requests from local health authorities) or if warranted by participant's history in accordance with Table 3.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of an AE, SAE, TEAE, and AESI can be found in Appendix 2. DLTs for Part 1 are defined in Section 4.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE, or AESI and remain responsible for following up all events.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs will be collected from the signing of the informed consent form (ICF)/assent until 30 days after the last dose of study treatment and SAEs will be collected from the signing of the ICF/assent until 90 days after the last dose of study treatment (or to a minimum of 30 days after the last dose of study treatment if the participant starts alternative anticancer treatment) at the time points specified in Table 3. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study treatment will be recorded from the signing of the ICF/assent through the Follow-up Assessment Period as specified in Table 3.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent/assent will be recorded as Medical History/Current Medical Conditions, not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, the investigator must record it in the medical records per the local country requirements. If the investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

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

Study site staff should instruct the legal guardians and caregivers on how to report signs and symptoms (e.g., crying and pain) in the individual paediatric participant. They will be instructed to report both specific and non-specific symptoms (including vomiting, diarrhoea, sleepiness, variation in the intensity and pattern of crying, etc.). These non-specific symptoms may be the only manifestations of some adverse reaction observed in children or adolescents. Care should be taken that the clinical presentation of adverse reactions is not misinterpreted as the manifestation of a pre-existing or unrelated condition.

Moreover, symptoms that are dependent on participant communication ability (e.g., nausea, pain, mood alterations) in younger or mentally disabled children could potentially be at risk for under- or misreporting.

8.3.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All ongoing AEs and SAEs will be followed, regardless of start of alternative anticancer therapy, until the event is resolved, stabilised, or otherwise explained or until the participant has withdrawn consent to the study overall, is lost to follow-up (as defined in Section 7.4), or has died. Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific 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 (eg, 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.
- Investigators have to report to the Sponsor pregnancies, medication errors, abuse and misuse even in an absence of an AE/SAE as these may be subjected to local regulatory reporting requirements for the Sponsor.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants who receive study treatment will be collected after the start of

study treatment and until 180 days after the last dose of study treatment in female participants and 90 days after the last dose of study treatment for female partners of male participants.

- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner). 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.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partners, the Investigator may learn of an SAE through spontaneous reporting.

8.3.6. Adverse Events of Special Interest (AESI)

AESIs must be recorded as such on the eCRF. The definitions of AESIs can be found in Appendix 2.

The following AESIs for niraparib should be reported to the Sponsor throughout the Treatment Phase of the study, Safety Follow-up, and the long-term Follow-up Assessment Period:

- MDS and AML
- Second primary malignancy

There are no AESIs for dostarlimab.

8.4. Pharmacokinetics, Immunogenicity, and Biomarkers

Blood samples to assess niraparib PK, dostarlimab PK, and dostarlimab ADAs and NAb will be collected from all participants pre- and postdose at the time points specified in Table 3. In addition, blood samples will be collected for exploratory biomarker analyses from participants with a body weight ≥12.5 kg and either neuroblastoma or osteosarcoma. The maximum blood volume for each sample for PK, ADA, NAb, and/or exploratory biomarker assessment is 0.8 mL/kg, and the maximum total blood volume allowed for PK, ADA, NAb, and/or exploratory biomarker assessments is 1.8 mL/kg per 3-week cycle.

In the event of concern for excessive blood volume withdrawal, sample collection should be prioritised as outlined in Section 8.2.

GSK may store samples for up to 20 years after the end of the study to achieve study objectives (including for genetic testing; Section 8.5). Additionally, with participants' consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of neuroblastoma or osteosarcoma or other diseases, the development of related or new treatments, or research methods.

8.4.1. PK Sample Collection

CCI [redacted], and blood (serum) samples for evaluation of dostarlimab concentrations will be obtained at the time points specified in Table 3. All PK samples once collected (regardless of dosing) may be analyzed if the sample date and time have been recorded, provided the necessary informed consent from the participant remains in effect.

Description of the PK analysis is summarised in Section 9.3.3.3.

8.4.2. Immunogenicity Sample Collection

Blood samples for the evaluation of dostarlimab ADAs and NAb with associated drug concentration will be obtained at the time points specified in Table 3. Serum samples for the determination of anti-dostarlimab antibodies will be aliquots of the same samples collected as for PK. ADAs will be analysed in a tiered approach (i.e., screening, confirmation, titre, and neutralising antibody assay) using electrochemiluminescence, if appropriate. Description of the immunogenicity analysis is summarised in Section 9.3.3.5.

CCI [redacted]

CCI

[redacted]

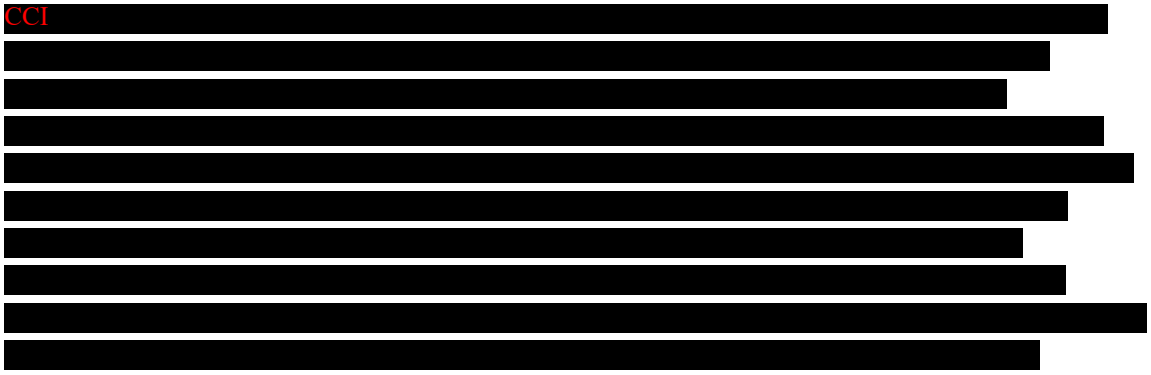
8.6. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalised prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated. There will be a detailed description of participant disposition; participant demographics and baseline characteristics will be summarised.



The detailed censoring rules for time-to-event variables will be included in the SAP. Additional statistical details for Part 2 of this study are presented in each cohort-specific supplement, as applicable.

9.1. Sample Size Determination

The sample size of approximately 56 participants in total is not based on formal statistical hypotheses, but is estimated based on an mTPI-2 dose escalation design for Part 1 including approximately 7 cohorts (4 cohorts planned in Part 1A under Protocol Amendment 03 and 3 cohorts planned in Part 1B under Protocol Amendment 05 [8 participants per each of the 7 cohorts]). Up to 5 additional participants may be enrolled to further evaluate the youngest participant group(s) if not represented.

9.2. Analysis Populations

For the purposes of analysis, the following analysis sets are defined as follows in Table 16.

Table 16: Analysis Sets

Participant Analysis Set	Description
Safety	The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
Intent-to-Treat (ITT)	The ITT Population includes all participants who receive any study medication and have measurable baseline tumour assessment and/or, for neuroblastoma participants, MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid tumours) at baseline.
Modified Intent-to-Treat (mITT)	The mITT Population includes all participants who receive any study medication, have measurable baseline tumour assessment, and/or, for neuroblastoma participants, MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid-tumours) at baseline, and have at least 1 postbaseline tumour assessment.
Per Protocol	The Per Protocol Population includes all participants in the mITT Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.
DLT-evaluable	The DLT-evaluable Population consists of participants in Part 1 who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT.
Pharmacokinetic (PK)	The PK Population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK Populations are defined separately for each agent.
Immunogenicity (ADA) Population	The ADA Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

Abbreviations: ADA=antidrug antibody; DLT=dose limiting toxicity; ITT=Intent-to-Treat; mITT=modified Intent-to-Treat; PK=pharmacokinetic.

9.3. Statistical Analyses

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1. General Considerations

Participant disposition will be tabulated and will include the number of screened participants (ie, participant or the participant's LAR, parent, or legal guardian has signed the ICF) and the number of participants in each study population for analysis, the number of participants who have discontinued treatment, and the reasons for treatment discontinuation.

Demographics, baseline characteristics, concomitant medications, and medical history information will be summarised using descriptive statistics.

All analyses will include summary statistics, including number of participants and percentage for categorical variables, and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs based on the Clopper-Pearson method will be provided where appropriate (Clopper, 1934). Time-to-event analyses will be performed using Kaplan-Meier methods.

The primary analysis set for the efficacy endpoints will be the mITT Population.

9.3.2. Primary Endpoints

For Part 1, the primary endpoint is DLTs. The incidence of DLTs will be summarised by study part and cohort for the DLT-evaluable Population.

9.3.3. Secondary Endpoints

9.3.3.1. Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined in Section 8.1.2.

The number and proportion of participants with an objective response will be tabulated by dose cohort and overall. ORR will be calculated, along with its estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR will be performed using Kaplan-Meier method, including quartile estimates and two-sided 95% CI.

9.3.3.2. Safety Analyses

For all parts of the study, additional safety data will be summarised for the Safety Population.

Study treatment duration and dose intensity will be summarised descriptively. The occurrence of dose interruption and dose modification will be tabulated.

AEs will be classified according to Medical Dictionary for Regulatory Activities (MedDRA) v20.0 or later. All AEs occurring during the study will be included in by-participant data listings and tabulated by MedDRA system organ class and preferred term. TEAE is defined as any AE with onset after the first administration of study treatment, throughout the Treatment Period, until 30 days after cessation of study treatment (90 days for SAEs) (or until the start of new anticancer treatment whichever occurs earlier), or any event that was present at baseline but worsened in intensity or was subsequently considered study treatment-related by the Investigator through the end of the study.

Safety parameters will include the incidence of TEAEs, related TEAEs, serious TEAEs, TEAEs of Grade 3 or greater by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5, TEAEs leading to death, TEAEs leading to treatment discontinuation, and TEAEs leading to dose modification. AESIs will also be summarised and listed. No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs occurring on study will be listed in participant data listings. By-participant listings also will be provided for the following: participant deaths, SAEs, and AEs leading to withdrawal of study treatment.

Clinical laboratory tests, vital signs, ECG results, physical examination findings, performance status, and concomitant medication usage will be listed per participant for each assessment, and descriptive statistics will be tabulated for selected safety parameters.

9.3.3.3. PK Analysis

The PK characteristics of niraparib and dostarlimab will be evaluated in the PK Population of this study using sparse blood sampling and population PK approaches. Serum concentrations of dostarlimab and CCI [redacted] will be presented using descriptive statistics by dose cohort and overall. Summary statistics will include mean, standard deviation, coefficient of variation (CV), geometric mean, geometric mean CV, median, and minimum and maximum values. The CCI [redacted] data may be used to evaluate the age-related development of niraparib metabolism in paediatric participants, if data permit. Niraparib and dostarlimab concentration-time data will be analysed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters and identify relevant covariates (e.g., age, weight, or disease-related covariates). The data from this study may be combined with data from other studies, which will be reported in a separate report.

In addition, if deemed appropriate and if data permit, exposure-response relationships between exposure (e.g., dose, dose intensity, concentration, maximum concentration, or area under the concentration-time curve) and clinical activity and/or toxicity (e.g., response, [exploratory] biomarkers, safety event) may be explored using population modelling approaches. If data permit, the effects of covariates may be explored. Results of such analysis will be reported in a separate report.

CCI [redacted]

CCI [redacted]

9.3.3.5. Immunogenicity Analysis

Immunogenicity of dostarlimab will be analysed only in the Immunogenicity Population. Minimally, ADA will be evaluated in all predose samples collected at each specified time point, as well as at EOT, at the Safety Follow-up Visit (30 days post-treatment), and at the first Follow-up Visit (90 days post-treatment). The number and percent of participants who become positive for ADAs and who develop NAb will be summarised by treatment, visit/time and overall.

9.3.4. Exploratory Endpoints

The exploratory endpoints may include the assessment of biomarkers related to PARP inhibition and/or anti-PD-1 therapy and correlation with clinical outcome, based on provision of blood samples collected on study. Descriptive statistics may be used to summarise the ORR, DCR, PFS, and DOR in participants of different biomarker subpopulations.

The data from this study may be combined with data from other studies and may be reported in a separate report.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The regulatory and ethical considerations of the study are outlined in Appendix 1.

11. APPENDICES

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY CONSIDERATIONS

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

CCI [redacted]

Informed Consent Process

- The Investigator or their representative will explain the nature of the study to the participant or their legally authorised representative (LAR) and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or their LAR.
- The Investigator must obtain assent from the minor participant in addition to the consent provided by the participants' parent(s)/LAR(s) when a minor can assent to participate in a study. The Investigator is also accountable for determining a minor's capacity to assent to participation in a research study according to the local laws and regulations.
- The assent process will be tailored to the age of the potential participant and to any circumstances around the participant's enrolment.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study treatments or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the study treatments approved for medical use or approved for payment coverage.

Recruitment Strategy

- Participants will be identified for potential recruitment using each research site's clinical database prior to consenting to take part in this study.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant/ participants' parent(s)/LAR(s) must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the

participant who will be required to give consent for their data to be used as described in the informed consent.

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- GSK will ensure protection of the personal data of the Investigator and site staff which is collected within the framework of and for the purpose of the study.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

Committees Structure

Early Safety Data Review AND/OR Committee

For Part 1 and Part 2 Safety run-in of the study, in accordance with the Sponsor's standard operating procedure, the DEC will monitor intervention-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of participants enrolled in this study as described in detail in the Dose Escalation Plan. The DEC will be chaired by the GSK Medical Monitor and membership will include a GSK clinical scientist, GSK safety physician, GSK statistician, GSK pharmacokineticist, along with additional GSK designated staff as appropriate, representatives from the supporting contract research organization, and all participating Investigators. The DEC will review relevant safety and PK data generated immediately after all participants treated in the same dose cohort have passed the DLT period and on an ad hoc basis, as mandated by emerging study data.

A data review committee (DRC) will be established for the purpose of monitoring safety and efficacy data from the Cohort Expansion part of the study (Part 2). The DRC may also take into consideration relevant findings from Part 1A and/or Part 1B if doing so would assist in review of data from Part 2. This committee will be composed of GSK staff who are independent of all aspects of the study. Members will include a clinical development physician, a safety physician, and a statistician. This committee will convene both periodically and on an ad hoc basis, as mandated by emerging study data. Comprehensive details of committee membership and its activities are described in a formal charter.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all Investigators who were involved in the study with the full summary of the study results, including a summary of trial results understandable to laypersons. The Investigator(s) is/are encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorisation by regulatory authorities.
- Where required by regulation, the names of the Sponsor signatory and Investigator signatory will be made public.
- GSK will provide the Investigator with participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect personal information; these measures will comply with data protection and privacy laws that apply. Requests for access may be made through www.clinicalstudydatarequest.com.
- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results and are

documented in the Clinical Monitoring Plan. These pre-defined parameters will be monitored during the study and deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process, including systems used, can be found in the Data Management Plan.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organisations [CRO]).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final Clinical Study Report (CSR)/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.

Source Documents

- For this study there may be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available). Data entered directly in the eCRF will be minimal and may include pregnancy information and results of COVID testing.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data and its origin can be found in the source data agreement.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Source data are shared with third parties contracted by GSK for external assessment or adjudication (e.g. endpoint adjudication committee; expert reader). Source data may also be shared, if necessary, with insurers. The non-exhaustive list of source data shared may include [discharge summaries, imaging reports, scans, pathology reports, biological specimens, ECG reports, lab reports, physician/consult notes, medication administration records; adverse event reports; safety monitoring reports; vital signs data, eCRFs; PK and biomarker data, etc.]. Participant names or any information that would make the participant identifiable or is not essential for the external assessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third-party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the Investigator.
- Total number of participants included earlier than expected.
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Publication Policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. GSK follows International Committee of Medical Journal Editors standards for authorship and uses good publications practices to guide publications.

APPENDIX 2. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (haematology, clinical chemistry), urinalysis (if obtained), or other safety assessments (e.g., ECG, radiologic 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).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant'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 participant's condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

Definition of SAE

An SAE is defined as any serious AEs 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 participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

In general, hospitalisation signifies that the participant has been admitted (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 hospitalisation are AE. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant 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, diarrhoea, influenza, and accidental trauma (eg, sprained ankle) which 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:

Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE.

Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardise the participant 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Definition of an Adverse Event of Special Interest

An AESI is any AE (serious or nonserious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate.

Niraparib AESIs

AESIs for niraparib are the following:

- Myelodysplastic syndrome (MDS) and AML
- Second primary malignancy (new malignancies [other than MDS or AML])

Dostarlimab AESIs

There are no AESIs for dostarlimab.

Definition of TEAE

TEAE Definition
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, except for the

AE and SAE Recording
participant number, will be redacted on the copies of the medical records before submission to GSK. • 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/SAE.
Assessment of Intensity
The severity of AEs will be graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5: 27 November 2017; National Institutes of Health (NIH), National Cancer Institute (NCI). The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of severity of each AE. The CTCAE v5 is available on the NCI/NIH website. In general, NCI-CTCAE severity grades are as follows: • Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; easily tolerated. • Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs; instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money). • Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL (self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and being not bedridden). • Grade 4: Life-threatening consequences; urgent intervention indicated. • Grade 5: Death related to AE. A distinction should be made between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria presented in the Section 'Definition of SAE'. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalisation for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.
Assessment of Causality
The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

AE and SAE Recording

- 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 treatment administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that they have 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 GSK. 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 GSK.**
- Where more than 1 intervention is administered in the same visit, the Investigator should specify, when possible, if the AE/SAE could be causally related to a specific study intervention. When a causal relationship to a specific study intervention cannot be determined, the Investigator should indicate the AE/SAE to be related to all interventions.
- The Investigator may change their 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 determining regulatory reporting requirements.

Assessment Of Outcomes

The Investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

Follow-up of AE and SAE

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as

requested by GSK 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.

- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

After the initial AE/SAE/AESI/pregnancy or any other event of interest, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, [and nonserious AESIs (as defined in the Section 8.3.6], will be followed until the event is resolved, stabilised, otherwise explained, or the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts as outlined in Section 8.3.

If a participant dies during their participation in the study or during a recognised follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants/pregnant partners of male participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the appropriate report form and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the Investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the Investigator to be reasonably related to the study intervention, to GSK as described in the Section 'Reporting of SAE to GSK'.

Updating of SAE, AESI, and pregnancy information after removal of write access to the participant's eCRF

When additional SAE, AESI, or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The

updated report should be sent to the study contact for reporting SAEs (refer to the Section 'Reporting of SAE to GSK').

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The Investigator or medically-qualified sub-Investigator must show evidence within the eCRF (eg, check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the CRO by telephone.
- Contacts for SAE reporting can be found in the local study contact information.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **Medical Monitor.**
- In rare circumstances and in the absence of 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 data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the local study contact information.

APPENDIX 3. CONTRACEPTION GUIDELINES

Definitions

Women in the following categories are considered WOCBP (fertile):

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

  Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Permanent sterilisation methods (for the purpose of this study) include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

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

Contraception Guidance

Table 17: Contraceptives Allowed During the Study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective Methods[b] that Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• IUD
• IUS[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomised or due to a medical cause) o Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note:** documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence **Note:** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Abbreviations: CTFG=Clinical Trial Facilitation Group; IUD=intrauterine device; IUS=intrauterine hormone-releasing system; LAM=lactational amenorrhoea method.
Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

APPENDIX 4. GUIDELINES FOR ASSESSMENT OF DISEASE, DISEASE PROGRESSION AND RESPONSE CRITERIA – ADAPTED FROM RECIST 1.1

Assessment Guidelines

Assessment guidelines based on RECIST 1.1 (Eisenhauer, 2009; Schwartz, 2016) are presented in the following sections.

Please note the following:

- The same imaging method, including use of contrast when applicable, must be used throughout the study to evaluate a tumour lesion for a given participant. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimetres (mm), using a ruler or callipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) is required.
- Fluorodeoxyglucose-positron emission tomography (FDG-PET) is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scan correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET or whole body MRI may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of metastatic bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules).

CT and MRI: **Contrast-enhanced CT with 5 mm contiguous slices is recommended.** Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used.

X-ray: In general, X-ray should not be used for target lesion measurements due to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are

clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray.

Brain Scan: If brain scan is required, then IV contrast-enhanced MRI is preferable to IV contrast-enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (ie, X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET (FDG or fluoride) may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of metastatic bone disease and PET is performed at all assessments.

Guidelines for Evaluation of Disease

Measurable and Non-Measurable Definitions

Measurable Lesion

A non-nodal lesion that can be accurately measured in at least 1 dimension (longest dimension) of:

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (eg, if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm calliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if:

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured.

Non-measurable Lesion

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: Leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Measurable Disease

The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilised as the only measurable lesion.

Baseline Definition of Target Lesions and Non-target Lesions

Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected based on their size (measurable diameters) and their suitability for accurate repeated measurements.

All other lesions or sites of disease should be recorded as non-target lesions at Screening/baseline and should be followed qualitatively. Non-target lesions can be grouped by organ. Measurements are not required; instead, the status of non-target lesions should be determined as "present," "absent"), or in rare cases, "unequivocal progression" during follow-up.

Additional guidance for selection of target lesions and non-target lesions at Screening/baseline is presented below:

- For selection of target lesions, paired organs such as the lungs or kidneys are each considered together as a single organ, and no more than 2 lesions should be recorded as target lesions within the pair. The skin and all lymph nodes are each considered a single organ for the purposes of target lesion selection.
- Lymph nodes of pathologic size with short axis diameters of 10 mm to <15 mm should be recorded as non-target lesions.
- Lesions identified by clinical assessment (superficial skin lesions) should only be followed as non-target lesions when other suitable target lesions are available.
- Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft-tissue components that can be evaluated by CT or MRI can be considered measurable (soft-tissue component). Bone scans, FDG-PET scans, or x-rays are not considered adequate imaging techniques to measure soft-tissue components of bone lesions.

Response Criteria

Evaluation of Target Lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (eg, percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the

smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.

- Not Evaluable (NE): Cannot be classified by one of the 5 preceding definitions. Only relevant if, at the follow-up tumour assessment, any of the target lesions were not assessed or were NE, and criteria for PD have not been met considering evaluable target lesions.

Notes:

- A sum of diameters is calculated from the long-axis diameters of non-nodal lesions and short axis diameters of lymph nodes (as applicable).
- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (i.e., sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status, then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.
- If a target lesion splits, the longest diameter (non-nodal)/short axis diameter (lymph node) of each portion should be measured and added to the target lesion sum of diameters.
- If target lesions merge and it is not possible to capture maximum diameter measurements for the individual lesions, the long-axis diameter (non-nodal)/short-axis diameter (lymph node) across the merged lesions should be recorded as the measurement for 1 of the merged lesions and 0 mm recorded for the other.

Evaluation of Non-Target Lesions

Definitions for assessment of **individual** non-target lesions **status**:

- **Present:** At the follow-up tumour assessment, the non-target lesions is still present and has not increased enough to warrant a status of unequivocal progression.
- **Absent:** This status should be used for non-nodal, non-target lesions that have disappeared at the follow-up tumour assessment and for lymph node non-target lesions that reduce to less than 10mm in short-axis diameter.
- **Unequivocal Progression:** At the follow-up tumour assessment, the non-target lesion showed unequivocal worsening/progression.
- **Unable to evaluate:** At the follow-up tumour assessment, the non-target lesion was not assessed (e.g. imaging did not cover the anatomical lesion location) or was NE (e.g., image quality was inadequate and the lesion could not be evaluated).

Definitions for collective assessment of response for all non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g., <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥10 mm short axis.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the 4 preceding definitions.

Notes:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (eg, non-target response does not have to be “Not Evaluable”).

New Lesions

New malignancies (i.e., new lesions) denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the Investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented. Note: the date of progression will be the date the unequivocal lesion was first identified as equivocal.

Evaluation of Overall Response

Table 18 presents the overall response at an individual time point for all possible combinations of tumour responses per RECIST v1.1 in target and non-target lesions with or without the appearance of new lesions for participants with measurable disease at baseline.

Table 18: Evaluation of Overall Response for Participants with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; NA=not applicable; NE=not evaluable; SD=stable disease.

Notes:

- Participants 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." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective 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 (fine needle aspirate/biopsy) to confirm the CR.

Confirmation Criteria

To be assigned a status of confirmed PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met. Please refer to the Tumour Assessment Flowchart Table 4) for information on imaging requirements for response confirmation.

APPENDIX 5. GUIDELINES FOR ASSESSMENT OF DISEASE, DISEASE PROGRESSION AND RESPONSE CRITERIA IN PARTICIPANTS WITH NEUROBLASTOMA – ADAPTED FROM REVISED INTERNATIONAL NEUROBLASTOMA RESPONSE CRITERIA (INRC)

A National Cancer Institute–appointed executive planning committee, selected a panel of 52 international Investigators from 13 countries with oncology, pathology, radiology, nuclear medicine, surgery, biology, and statistical expertise to develop and implement a revised consensus response criteria for neuroblastoma (Park, 2017).

Assessment Guidelines:

- Anatomic imaging (CT/MRI) will be used for defining measurable primary tumour sites and soft tissue metastatic lesions (non-lymph node tumour lesions and malignant lymph nodes) and response in accordance with RECIST criteria (Refer to Appendix 4 Assessment Guidelines and Definitions of Measurable Lesions).
- Nuclear medicine imaging with iodine-123 (123I) MIBG-single-photon emission computed tomography (SPECT) or MIBG-SPECT/CT will be used to inform measurable lesions and assess primary and metastatic soft tissue and osteomedullary lesion response in participants with MIBG-avid tumours.
- [18F] fluorodeoxyglucose (FDG) –positron emission tomography (PET) will be used as an alternative modality for tumour detection in participants whose tumours do not concentrate MIBG.

Note: The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate disease. (eg. CT and/or MRI plus MIBG-SPECT, or CT and/or MRI plus FDG-PET)

- Bilateral bone marrow aspirates and trephine biopsies for assessment of marrow disease using morphologic criteria in conjunction with appropriate antibodies to confirm the identity of neuroblastoma cells by immunocytology (if available) and/or immunohistochemistry at screening/baseline and to evaluate response during treatment, if positive at baseline.

Guidelines for Evaluation of Disease

Primary and Metastatic Soft Tissue Disease

MIBG-SPECT/CT (or FDG-PET/CT, if tumour is MIBG-nonavid) in conjunction with CT/MRI should be used to evaluate soft tissue lesions.

Target lesions: Disease sites that meet criteria of measurable size (nonlymphoid soft tissue mass ≥10 mm in longest dimension or lymph node ≥15mm in short axis) as well as either uptake on MIBG (or FDG for MIBG non-avid tumours) or biopsy positive for neuroblastoma or ganglioneuroblastoma.

Non-target lesions: Lesions that are considered to be active tumour sites but do not meet target lesion criteria; include leptomeningeal tumour; tumour in cerebrospinal fluid,

ascites, or pleural effusion, and lesions smaller than 10 mm that are considered likely to be active tumour based on clinical correlation (eg, hepatic and pulmonary nodules); small (<10 mm) soft tissue lesions and lymph nodes that measure shorter than 15 mm on short axis will be considered non-target lesions if they are biopsied and proven to consist of viable tumour.

Note: Non-lymph node soft tissue lesions at least 10 mm in diameter and lymph nodes larger than 15 mm on short axis that are not MIBG or FDG-avid and do not contain viable tumour (if biopsied) will not be considered either target or non-target lesions.

Metastatic Bone Disease:

Osteomedullary lesions should be evaluated using MIBG-SPECT/CT imaging, or FDG-PET/CT for participants with MIBG non-avid disease. Anatomic imaging will not be used to evaluate osteomedullary lesions.

MIBG semiquantitative scoring systems will be used for response assessment in bone lesions with 123I-MIBG uptake. Relative score on bone sectors should be used for response assessment (absolute score of bone lesions at time of assessment divided by absolute score of bone lesions at screening/baseline).

The same scoring method [eg, Curie (Matthay, 2003), International Society of Pediatric Oncology European Neuroblastoma (SIOPEN) (Ady, 1995)] and the same imaging modality (MIBG-SPECT, or FDG-PET for participants with MIBG non-avid disease) should be used for all evaluations.

Note: Extramedullary soft tissue components of bone lesions should be assessed following guidance for other soft tissue sites.

Metastatic Bone Marrow Disease:

All sites of bone marrow involvement, including level of involvement (percentage of tumour infiltration of bone marrow space assessed by histologic evaluation of trephine or biopsy or counting of the number of tumour cells in aspirates divided by the number of haematopoietic or mononuclear cells evaluated to obtain a percentage of involvement) should be reported.

In the case of discrepant results between aspirations or core biopsies from 2 or more sites taken at the same time, the highest infiltration result should be reported.

Response Criteria

Evaluation of Primary (Soft Tissue) Tumour Response:
Criteria for response in primary tumour using anatomic + MIBG (FDG-PET) imaging are provided in Table 19.

Table 19: Primary (Soft Tissue) Tumour Response [a]

Response	Definition
CR	<10mm residual soft tissue at primary site and complete resolution of MIBG or FDG uptake at primary site
PR	≥30% decrease in longest diameter of primary site and MIBG or FDG uptake at primary site stable, improved, or resolved
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD at the primary site
PD	>20% increase in longest diameter taking as reference the smallest sum on study (including baseline sum) and minimum absolute increase of 5mm in longest diameter [b]

Abbreviations: CR=complete response; FDG=[^{18}F]fluorodeoxyglucose; MIBG = metaiodobenzylguanidine; PD=progressive disease; PET=positron emission tomography; PR=partial response; SD=stable disease.

a. Not for use in assessment of metastatic sites.
b. Mass that does not meet PD measurement criteria but has fluctuating MIBG avidity will not be considered PD.

Evaluation of Tumour Response at Metastatic Soft Tissue and Bone Sites

Criteria for response in soft tissue (including lymph node and non-lymph node) and bone metastases using anatomic + MIBG (FDG) imaging are provided in Table 20.

Table 20: Tumour Response at Metastatic Soft Tissue and Bone Sites

Response	Definition
CR	Resolution of all sites of disease, defined as: • Nonprimary target and non-target lesions measure <10 mm AND • Lymph nodes identified as target lesions decrease to a short axis <10 mm AND • MIBG uptake or FDG uptake (for MIBG-nonavid tumours) of nonprimary lesions resolves completely
PR	≥30% decrease in sum of diameters[a] of nonprimary target lesions compared with baseline AND all of the following: • Non-target lesions may be stable or smaller in size • No new lesions • ≥50% reduction in MIBG absolute bone score (relative MIBG bone score ≥0.1 to <0.5) or ≥50% reduction in number of FDG-avid bone lesions [b, c]
SD	Neither sufficient shrinkage for PR nor sufficient increase for PD of nonprimary lesions
PD	Any of the following: • Any new soft tissue lesion detected by CT/MRI that is also MIBG-avid or FDG-avid • Any new soft tissue lesions detected by CT/MRI that has been biopsied and confirmed to be neuroblastoma or ganglioneuroblastoma • Any new bone site that is MIBG-avid • A new bone site that is FDG-avid (for MIBG-nonavid tumours) AND has CT/MRI findings consistent with tumour OR has been confirmed histologically to be neuroblastoma or ganglioneuroblastoma • >20% increase in longest diameter taking as reference the smallest sum on study (including baseline sum) and minimum absolute increase of 5mm in sum of longest diameters of target soft tissue lesions • Relative MIBG score >1.2 [c]

Abbreviations: CR=complete response; FDG=[18F]fluorodeoxyglucose; MIBG= metaiodobenzylguanidine; PD=progressive disease; PET=positron emission tomography; PR=partial response; SD=stable disease; CT=computed tomography; MRI= magnetic resonance imaging.

a. Sum of diameters is defined as the sum of the short axis of discrete lymph nodes (ie, cervical, axillary nodes) added to the sum of the longest diameters of non-lymph node soft tissue metastases. Masses of conglomerate nondiscrete lymph nodes will be measured using longest diameter.

b. For participants with soft tissue metastatic disease, resolution of MIBG and/or FDG uptake at the soft tissue sites is not required; all size reduction criteria must be fulfilled.

c. Relative MIBG score is the absolute score for bone lesions at time of response assessment divided by the absolute score for bone lesions at baseline before therapeutic interventions. The same scoring method (eg, Curie or SIOPEN) must be used at all assessment time points

Evaluation of Metastatic Bone Marrow Disease

Criteria for response in bone marrow metastasis using cytology/histology are provided in Table 21.

Table 21: Metastatic Bone Marrow Disease

Response	Definition (Cytology†/Histology‡)
CR	Bone marrow with no tumour infiltration on reassessment, independent of baseline tumour involvement
PR	Any of the following: • Bone marrow with ≤5% tumour infiltration and remains > 0 to ≤ 5% tumour infiltration on reassessment • Bone marrow with no tumour infiltration that has ≤ 5% tumour infiltration on reassessment • Bone marrow with >20% tumour infiltration that has > 0 to ≤ 5% tumour infiltration on reassessment
SD	Bone marrow with tumour infiltration that remains positive with > 5% tumour infiltration on reassessment but does not meet CR, MD, or PD criteria
PD	Any of the following: • Bone marrow without tumour infiltration that becomes > 5% tumour infiltration on reassessment • Bone marrow with tumour infiltration that increases by > two-fold and has >20% tumour infiltration on reassessment

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; MD=minimal disease.
†Accompanied by immunocytology (recommended, not mandatory).
‡Accompanied by immunohistochemistry, specific recommendations included in article by Burchill, 2016.

Evaluation of Overall Response

Table 22 presents potential overall responses for all possible combinations of tumour responses in primary soft tissue, metastatic soft tissue and bone sites, and metastatic bone marrow disease.

Table 22: Evaluation of Overall Response

Response	Criterion
CR	All components meet criteria for CR
PR	PR in at least one component and all other components are either CR, MD* (bone marrow), PR (soft tissue or bone), or NI†; no component with PD
MR	PR or CR in at least one component but at least one other component with SD; no component with PD
SD	SD in one component with no better than SD or NI† in any other component; no component with PD
PD	Any component with PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; MR=minor response.
*For bone marrow assessment only.
†Site not involved at study entry and remains uninvolved.

Confirmation Criteria

To be assigned a status of confirmed PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met. Please refer to the Tumour Assessment Flowchart (Table 4) for information on imaging requirements for response confirmation.

APPENDIX 6. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 23: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA(s)	antidrug antibody(ies)
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
API	Active pharmaceutical ingredient
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BLA	Biologics License Application
BOR	best overall response
CCI [redacted]	
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
Cmin	minimum plasma concentration
CMAA	Conditional Marketing Authorisation Application
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CO2	Carbon dioxide
CR	complete response
CRF	case report form
CRO	contract research organisation
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	

Abbreviation or Specialist Term	Explanation
CTR	Clinical Trials Regulations
CV	coefficient of variation
CYP	cytochrome P450 enzyme
DCR	disease control rate
DEC	Dose Escalation Committee
DL-1	dose level -1
DL1	dose level 1
DL2	dose level 2
DLT	dose limiting toxicity
DRC	Data Review Committee
DRESS	Drug reaction with eosinophilia and systemic symptoms
dMMR	mismatch repair-deficient
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOT	End of Treatment
EU	European union
FDA	Food and Drug Administration
FDG-PET/CT	fluorodeoxyglucose-positron emission tomography/computed tomography
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HbcAB	hepatitis B core antibody,
HBsAg	hepatitis B surface antigen;
HBV	HBV = hepatitis B virus;
HCV	HCV=hepatitis C virus;
HR	hazard ratio
CCI [redacted]	
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
INRC	International Neuroblastoma Response Criteria
imAE	immune-mediated adverse event
imAEI	immune-mediated adverse event of interest
IRB	Institutional Review Board
IRR	Infusion-related reactions
IV	intravenous
K	Potassium
LAR	legally authorised representative
mAb	monoclonal antibody
MATE	multidrug and toxin extrusion transporter
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIBG-SPECT/CT	metaiodobenzylguanidine-single-photon emission computed tomography/computed tomography
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MSI-H	high microsatellite instability
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
mTPI-2	modified toxicity probability interval-2
Na	Sodium
NAb	neutralising antibody(ies)
NCI	National Cancer Institute
NE	not evaluable
NIH	National Institutes of Health
NSAIDS	Nonsteroidal anti-inflammatory drugs
ORR	objective response rate
PARP	poly (adenosine diphosphate-ribose) polymerase
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS6	progression-free survival rate at 6 months

Abbreviation or Specialist Term	Explanation
PK	pharmacokinetic(s)
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
Q6W	every 6 weeks
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	quality tolerance limit
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SJS	Stevens-Johnson Syndrome
SoA	schedule of activities
SPECT	single-photon emission computed tomography
STING	stimulator of interferon genes
$t_{½}$	half-life
T3	triiodothyronine
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TfOS	tablet for oral suspension
t_{max}	time to maximum plasma concentration
CCI [redacted]	
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPM	unit probability mass
US	United States of America
WHO	Word health organisation
WMA	World Medical Association
WOCBP	woman of childbearing potential

Definition of Terms

Term	Definitions
Adverse Drug Reaction (ADR)	An AEs where a causal relationship between a medicinal product and the AEs is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or nonserious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorised.
AxMP	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, i.e., medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorised AxMP = Medicinal product authorised in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorised AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorised AxMP = Medicinal product not authorised in accordance with Regulation (EC) No 726/2004 Safety reporting for unauthorised AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Investigational Product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Legal guardian	Parent(s) (preferably both if available or as per local requirements), legally appointed guardian(s), or LARs, as defined by national and local laws and regulations, who consent(s) on behalf of the minor. For the purposes of this study, all references to informed consent and assent refer to the paediatric participant (child) and his or her legal guardian who have provided consent (and assent as applicable), according to the Informed Consent Process and Assent form described in the Informed Consent Process section.

Term	Definitions
NIMP	A NIMP is a medicinal product that is not classified as an IMP in a study, but may be taken by participants during the study, e.g., concomitant or rescue/escape medication used for preventive, diagnostic, or therapeutic reasons or medication given to ensure that adequate medical care is provided for the participant during a study.
Paediatric participant	Minor child participating in research study.
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.
Serious Adverse Reaction	All noxious and unintended responses to an IMP related to any dose administered that result in death, are life-threatening, require patient hospitalisation or prolongation of existing hospitalisation, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.
Suspected unexpected serious adverse reaction	A suspected unexpected serious adverse reaction is a serious adverse reaction whose nature, severity or outcome is not consistent with the reference safety information.

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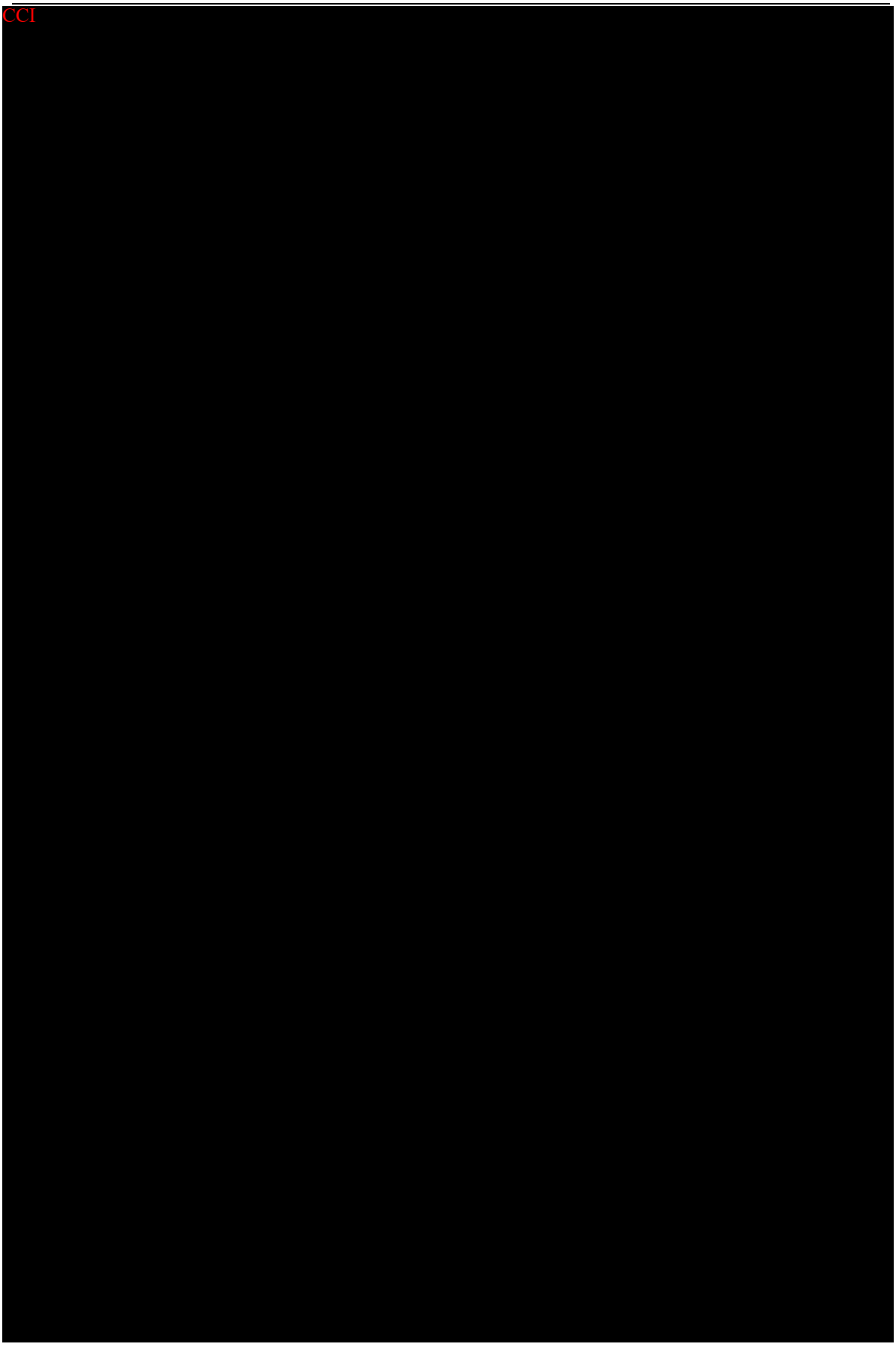

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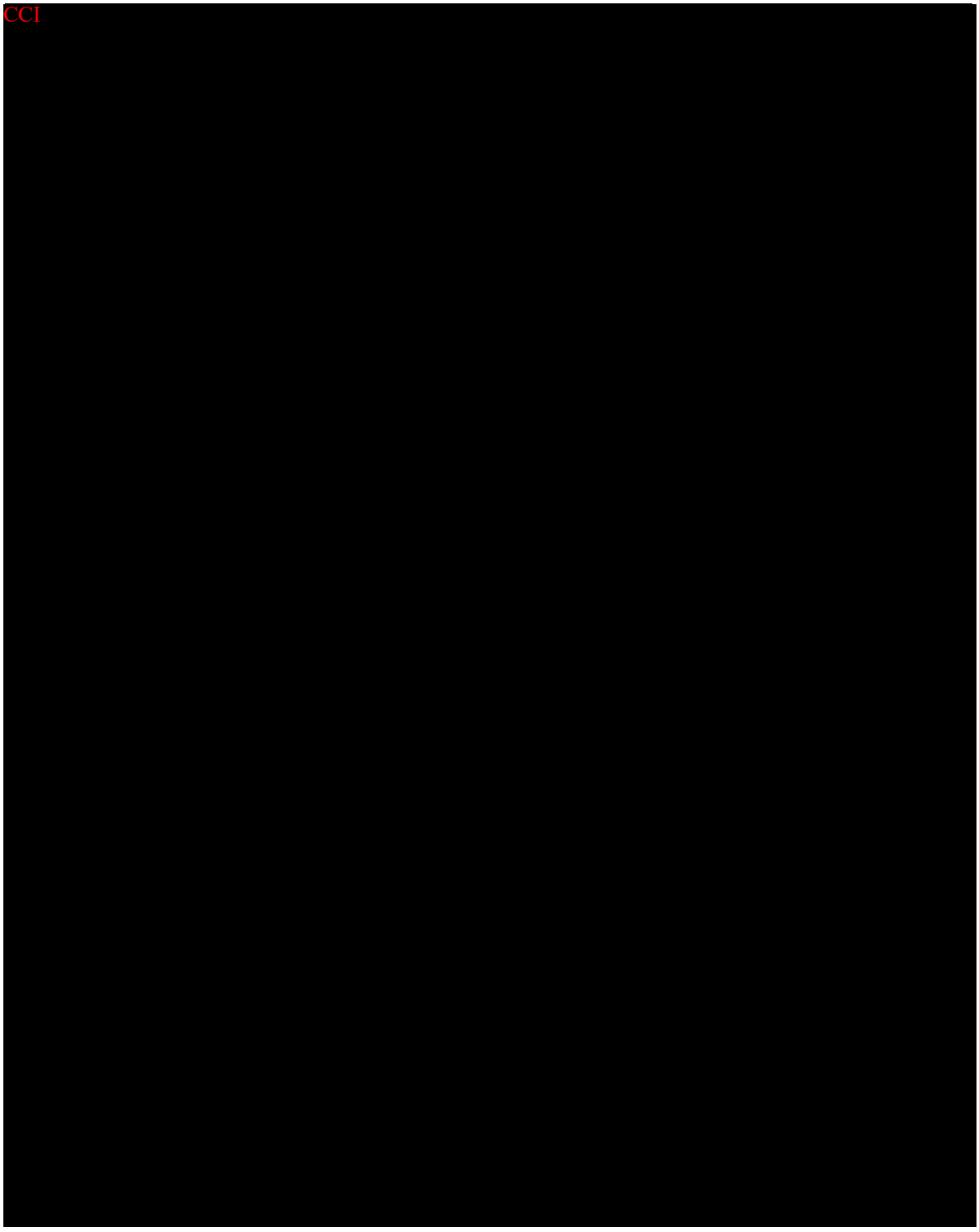

APPENDIX 8. LIVER SAFETY: REQUIRED ACTIONS, MONITORING, AND FOLLOW-UP TO ASSESS CAUSALITY OF LIVER EVENT

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

Table 24: Required actions, monitoring, and follow-up to assess causality of liver event

Liver event study intervention stopping criteria	
ALT absolute	Both ALT ≥5xULN and ≥2x baseline value
ALT increase	Unable to monitor weekly for 4 weeks: Both ALT ≥3xULN and ≥1.5x baseline value Able to monitor weekly: Both ALT ≥3xULN and ≥1.5x baseline value that persists for 4 weeks. Note: if values reduce to <3xULN and <1.5 x baseline or return to within baseline or normal limits for 2 consecutive weekly assessment, weekly monitoring may return to regular per protocol schedule.
Bilirubin[1, 2]	ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value).
INR[2]	ALT ≥3xULN and INR >1.5
Symptomatic[3]	Both ALT ≥3xULN and ≥1.5x baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

Required actions, monitoring and follow-up to assess causality of liver event	
Actions and monitoring	**Follow-up to assess causality of liver event**
• Immediately discontinue study intervention. • Report the event to GSK within 24 hours. • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[2]. • Perform liver event follow-up to assess causality of liver event. • Monitor the participant liver chemistries (see MONITORING). **MONITORING:** If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up to assess liver event causality within 24 hours. • Monitor participants twice weekly until liver chemistries reduce to <3xULN for ALT, <2xULN for total bilirubin or≤1.5 for INR or return to or remain within baseline or normal limits. • A specialist or hepatology consultation is recommended.	• Viral serology[4]. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG (IgG or gamma globulins). • Blood and serum sample for PK analysis of niraparib and dostarlimab, respectively, obtained within 144 hours after last dose of study intervention[5]. • Serum CPK and LDH, GGT, GLDH, and serum albumin. • Fractionate bilirubin, if total bilirubin ≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form.

For all other criteria (total bilirubin <2xULN and INR ≤1.5): • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up to assess liver event causality within 24-72 hours. • Monitor participants weekly until liver chemistries reduce to <3xULN for ALT or return to or remain within baseline or normal limits. **RESTART and/or RECHALLENGE** • Restart and/or rechallenge is allowed per protocol but do not resume study intervention unless GSK approval is granted. If restart and/or rechallenge is not granted, permanently discontinue study intervention and continue participant in the study for any protocol-specified follow-up assessments. Refer to Restart and/or Rechallenge guidelines in Appendix 9.	**If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above:** • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury. • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease, complete liver imaging form. • Liver biopsy may be considered and discussed with local specialist if available, for instance: – In patients when serology raises the possibility of AIH. – In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention. – In patients with acute or chronic atypical presentation. • If liver biopsy conducted, then complete liver biopsy form.

AIH = Autoimmune hepatitis; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CPK = Creatine phosphokinase; CRF = Case report form; DNA = Deoxyribonucleic acid; DILI = Drug-induced liver injury; GGT = Gamma glutamyl transferase; GLDH = Glutamate dehydrogenase; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HDV = Hepatitis D virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M; INR = International normalised ratio; LDH = Lactate dehydrogenase; PCR = Polymerase chain reaction; PK = Pharmacokinetic; RNA = Ribonucleic acid; SAE = Serious adverse event; ULN = Upper limit of normal.

1. Serum bilirubin fractionation should be performed if testing is available. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A IgM antibody; HBsAg and HBcAb (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant known to be HBsAg and/or HBcAb positive prior to onset of the liver event or subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed and if this is feasible).
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood or serum sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

Table 25: Liver Safety: Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Treatment – Liver Monitoring Event	
Criteria	**Actions**
• ALT ≥3×ULN and ≥ 1.5x baseline value and not meeting stopping criteria, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks.	• Notify the GSK Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment. • Participant must return weekly for repeat liver chemistries (ALT, AST, ALP, total bilirubin, and INR) until they stabilise until they stabilise (i.e., ALT or AST <3xULN and <1.5x baseline, and no increases in total bilirubin and INR) or return or remain to within baseline or normal limits. • If at any time participant meets the liver chemistry stopping criteria, proceed as described above. • If, after 4 weeks of monitoring, stopping criteria have not been met but any of the monitored liver chemistry (ALT, AST, alkaline phosphatase, total bilirubin and INR) remains abnormal/above baseline, monitor participants twice monthly until they stabilise or return to within baseline or normal limits. Alternatively, the monitoring can return to standard as per protocol when the Investigator and Medical Monitor agree that values are stable or no longer significantly abnormal (this may require local investigation of potential causes for liver chemistry abnormality).

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; GSK= GlaxoSmithKline; INR = International normalised ratio; ULN=upper limit of normal

APPENDIX 9. LIVER SAFETY DRUG RESTART OR RECHALLENGE GUIDELINES

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless per protocol or:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant

If GSK Medical Governance approval to restart/rechallenge participant with study treatment **is not granted**, then participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** (Andrade, 2009). Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity (Andrade, 2009) with initial liver injury (e.g., fever, rash, eosinophilia)
- jaundice or bilirubin >2×ULN with initial liver injury (direct bilirubin >35% of total)
- participant currently exhibits severe liver injury defined by: ALT >3×ULN, bilirubin >2×ULN (direct bilirubin >35% of total), or INR>1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges (Hunt, 2010; Papay, 2009)
- evidence of drug-related preclinical liability (e.g., reactive metabolites; mitochondrial impairment) (Hunt, 2010)

Rechallenge refers to resuming study treatment following drug-induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a participant who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment has been obtained, if required.

If the rechallenge is approved by GSK Medical Governance in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Appendix 2.

Restart Following Transient Resolving Liver Stopping Events Not Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g., biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, restart is not permitted following liver stopping event when the underlying cause was alcohol-related hepatitis.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5×baseline and ALT <3×ULN).
- Possible study intervention-induced liver injury has been excluded by the principal Investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study intervention has an identified genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study intervention-related liver injury cannot be excluded, the guidance on rechallenge in Section 7.1 will apply
- There is no evidence of alcohol-related hepatitis.
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.

If restart of study treatment is approved by GSK Medical Governance in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Participants approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.
- If after study treatment restart, participant meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- GSK Medical Monitor, and the Ethics Committee or Institutional Review Board, must be informed of the participant's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Appendix 2.

APPENDIX 10. MTPI-2 DESIGN

The dose escalation and de-escalation will be guided by the modified toxicity probability interval-2 (mTPI-2) design (Guo, 2017). The study team will use mTPI-2 spreadsheet and relevant pharmacokinetic information to make the final dose escalation, de-escalation, and appropriate dose decision for the next dose level.

Modified toxicity probability interval (mTPI) is an interval-based Bayesian design for dose finding (Ji, 2013). It utilises a Bayesian model to make escalation decisions based on the observed dose-limiting toxicities (DLTs) from the current dose level. Extensive simulation studies in literature have shown that, compared to a traditional rule-based design like 3+3, mTPI has favourable operational characteristics. In general, mTPI can more accurately select the maximum tolerated dose (MTD). Meanwhile, mTPI maintains a similar safety profile to designs like 3+3 in that the probabilities of overdosing are comparable. Moreover, mTPI is as transparent as methods like 3+3 in that all the dose finding decisions are precalculated in a spreadsheet before the study starts. Additionally, mTPI has the flexibility in the number of participants to be enrolled in a dose cohort.

In order to improve the mTPI dose finding performance in a small sample size, which is typically the case in a dose finding study, Guo et al developed the mTPI-2 design to overcome the Ockham's razor issue in the mTPI design that may lead to undesirable dose finding decisions from a safety perspective. Guo et al have shown that mTPI-2 has improved the mTPI performance in small sample size scenarios (Guo, 2017).

mTPI-2 Design

In this study, the target probability of DLT is chosen as 0.3, and the proper dosing toxicity interval is defined as (0.3-0.04, 0.3+0.04)=(0.26, 0.34). That is, any dose with a true probability of DLT falling in the proper dosing interval is consider as a candidate for the MTD. The underdosing interval is defined as a toxicity interval of (0, 0.26). The overdosing interval is defined as a toxicity interval of (0.34, 1.00). In order to perform the mTPI-2 evaluation, the underdosing and overdosing intervals are further divided into the following subintervals:

- underdosing subintervals: (0, 0.02), (0.02, 0.10), (0.10, 0.18), and (0.18, 0.26)
- overdosing subintervals: (0.34, 0.42), (0.42, 0.50), (0.50, 0.58), (0.58, 0.66), (0.66, 0.74), (0.74, 0.82), (0.82, 0.90), (0.90, 0.98), and (0.98, 1)

For each dose level, an uninformative prior distribution Beta (1,1) is assigned to the probability of DLT. After treating participants at a given dose level and collecting DLT data, we use Bayesian methods to derive the posterior distribution for the probability of DLT. Then, for each of the proper dosing intervals, underdosing subintervals, and overdosing subintervals, we calculate the unit probability mass (UPM): posterior probability of the interval divided by the length of the interval. Then we identify the interval with the maximum UPM, as follows:

- If the maximum UPM is from one of the underdosing subintervals, escalate the dose.
- If the maximum UPM is from the proper dosing interval, stay on the current dose.

- If the maximum UPM is from one of the overdosing subintervals, de-escalate the dose.

Table 26 shows the mTPI-2 decision spreadsheet based on a 0.3 target probability of DLT and a proper dosing toxicity interval (0.26, 0.34). The spreadsheet is produced for a dose cohort up to 30 participants and applies to every dose cohort. The spreadsheet was generated from the mTPI-2 online tool at http://www.compgenome.org/NGDF.

Table 26: mTPI-2 Decision Spreadsheet

Number of DLTs	Number of Patients																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU	D	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	S	E	E	E	E	E	E	E
7							DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	S	S	S	S	S	S	S	E	E	E
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9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	S	S	S	S
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	S
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D
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30																														DU

Abbreviations: D=de-escalation; DLT=dose limiting toxicity; DU=unacceptable dose; E=escalation; mTPI-2=modified toxicity probability interval-2; S=stay at the same dose.

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[redacted]

APPENDIX 12. CONSIDERATIONS FOR PARTICIPANTS WITH PAST HBV INFECTION

Management of Participants With Past HBV Infection

- Management by an HBV specialist is required. If a participant is not currently followed by a specialist, care should be established at the start of the study, prior to the first dose.
- Participants should be monitored for HBV reactivation according to Table 27.
- Participants who experience clinically significant elevations in liver chemistries meeting liver event monitoring and/or liver stopping criteria should, **in addition** to the actions outlined in Section 7.1.1, Appendix 8, and Appendix 9 undergo immediate and careful evaluation of etiology including HBV DNA, HBsAg and Hepatitis D Virus testing.
- Participants receiving dostarlimab who develop a dostarlimab-related adverse event requiring steroid treatment (Table 11) should be evaluated by an HBV specialist to determine whether HBV reactivation prophylaxis is required.

HBV Reactivation

- HBV reactivation in participants with past HBV infection is defined as one of the following:
  - HBV DNA is detectable or
  - Reverse HBsAg seroconversion occurs (reappearance of HBsAg)
- **Participants who develop HBV reactivation should:**
  - **Permanently discontinue study intervention, rechallenge is not permitted**
  - **Immediately refer to HBV specialist for urgent treatment initiation**
  - **Notify Medical Monitor within 24 hours**
  - **Repeat laboratory testing (HBV DNA, liver chemistries, INR and albumin) within 1-2 weeks to assess clinical course**

Additional Procedures for Past HBV Infection

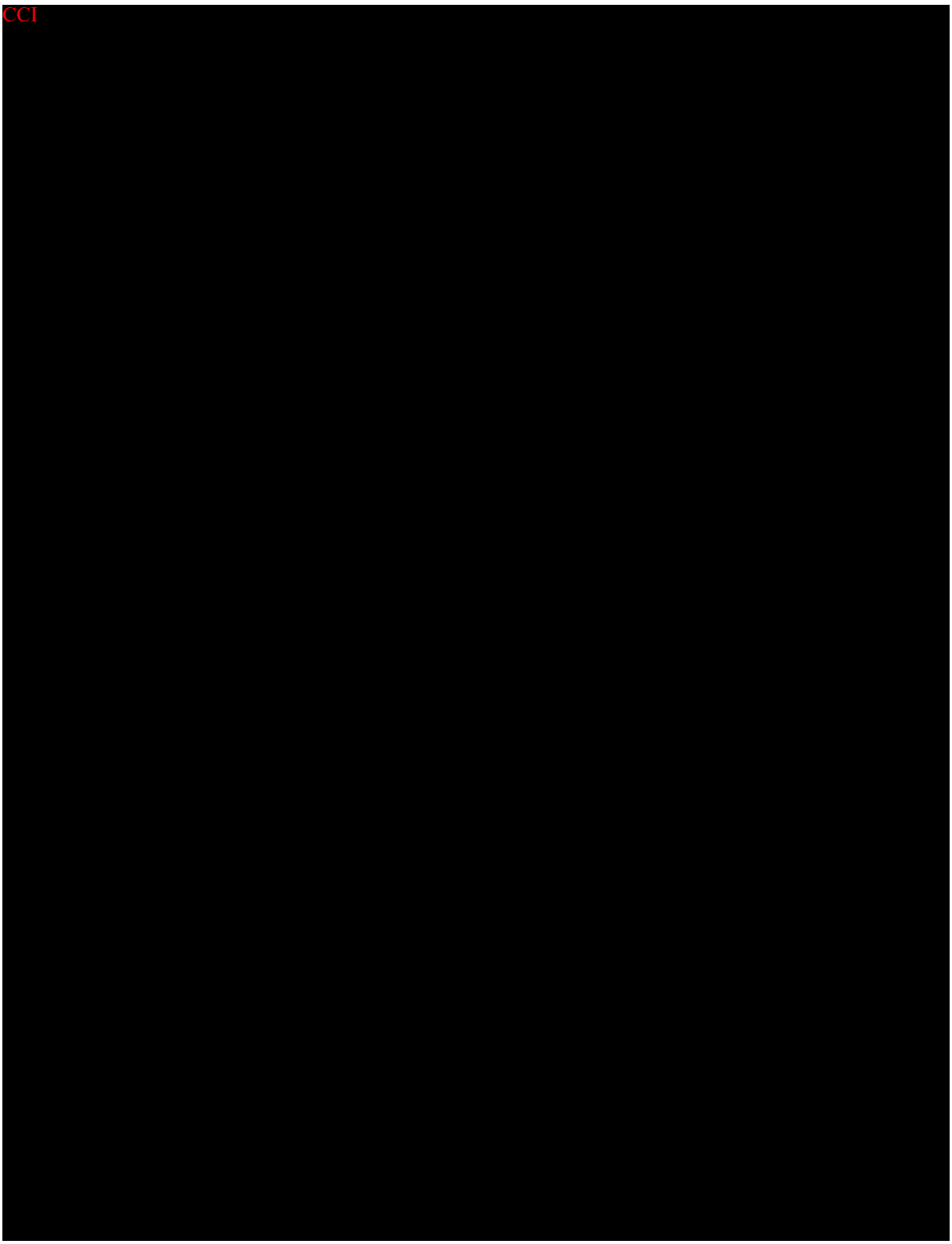
The procedures listed in Table 27 apply ONLY to participants in screening who have been enrolled and who have a past HBV infection (HBsAg negative, anti-HBcAb positive, HBV DNA negative); all procedures must be done as needed **in addition** to the required procedures for all participants detailed in the SoA (Section 1.3).

Table 27: HBV Schedule of Activities

HBV study assessments	During Screening/ prior to starting study intervention	Every 3 months during Treatment Period	EOT	90-day Safety Follow-up
HBV DNA testing	X	X[a]	X	X
HBsAg testing	X	X[a]	X	X

Abbreviations: DNA = deoxyribonucleic acid; EOT = end of treatment; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus

a. Participants should receive testing every 3 months with other predose safety labs, or if liver chemistry elevations requiring increased liver monitoring or stopping criteria occur, or for any clinical suspicion of HBV reactivation.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APPENDIX 14. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 01 (16 October 2020)

Overall Rationale for Amendment 01

Amendment 01 revised the protocol requirement for tumour assessments to be aligned with current standard of care and provides other clarifications and editorial changes catalogued since the issuance of the prior version of the protocol. Additionally, minor changes to the time allowed for safety reporting to ensure consistency with GSK standard practices. Changes for Amendment 01 are shown in Table 2.

Summary of Changes for Amendment 01

Table 2: Summary of Changes for Amendment 01

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this version.	Editorial changes to align with the Sponsor's standard protocol template and ways of working and inclusion of specific language noted during Health Authority review
Section 1.1. Synopsis	Addition of cross-reference to study design schema	Additional information included for ease of reading
Section 1.3. Schedule of Activities	Revision to footnote for vital signs assessment to include guidance for blood pressure monitoring	Alignment with niraparib safety monitoring in accordance with Investigator's Brochure, and Package Insert/Summary of Product Characteristics

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 1.3 Schedule of Activities Table 4: Tumour Assessment Flowchart Section 4.1.3 General Study Conduct Section 8.1.2.1. Timing of Radiologic Evaluations Appendix 5. List of Abbreviations and Definitions	Revision of preferred imaging types and schedule for scans; additionally, Schedule of Activities revised to separate imaging assessments according to different timings for standard of care and type of assessments	Allowable imaging types and schedule revised to align with current standard of care
Section 2.4. Rationale for Tumour Type	Deletion of duplicated reference	Typographical error
Section 1.1 Synopsis Section 4.1.1. Part 1A Design	Clarification of DLT criteria that facilitates dosing strategy by Dose Escalation Committee	Clarification to align protocol language with expected design plan
Section 4.1.2.1. Intra-participant Dose Escalation	Language revised to limit intra-participant dose escalation to Part 1A and limit escalation to one dose level higher	Revision to provide more specific instruction
Section 1.1. Synopsis Section 4.1.2. Part 1B Design	Inclusion of language to align the PK exposure to the RP2D	Addition to provide further clarity to determination of the RP2D
Section 1.1. Synopsis Section 1.3 Schedule of Activities Section 4.1. Part 1 Dose Escalation Design Section 8.4. Pharmacokinetics, Immunogenicity, and Biomarkers	Deletion of minimum body weight criteria for PK parameters	Deletion of information inadvertently propagated throughout protocol in error

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		CCI [redacted] Revision to align with standard of care Revised safety monitoring guidance
	Minimum threshold of performance status reduced to 60% in Inclusion #4 Criteria for adequate CBC collection result revised to 1 week in Inclusion #5 Minimum threshold of absolute neutrophil count reduced to ≥1,000/µL in Inclusion #5	
Section 1.1. Synopsis Section 8.1.3. PK Endpoints Section 9.3.3.3. Secondary Endpoints	PK Parameters revised to provide more specificity to the modelling intended for use and to remove the specific parameters	Revision of the information to more appropriately capture the components that will impact the statistics and remove detailed parameters as more appropriate within an analysis plan
Section 1.1. Synopsis Section 8.4. Pharmacokinetics, Immunogenicity and Biomarkers Section 9.2. Analysis Populations	Immunogenicity populations included	Provided for clarity as to analysis populations intended to be studied
Section 1.2. Schemas Section 4.1. Part 1 Dose-Escalation Design	Part 1A schemas revised to remove niraparib from PK assessment and footnote describing criteria for opening of cohorts added	Greater alignment with the protocol-described study design and

Section(s) Affected	Description of Change	Brief Rationale
Section 4.1.2.2. Dose Limiting Toxicity Section 4.4. Dose Adjustment Criteria Section 4.4.1. Dose Adjustment Criteria - Niraparib	Inclusion of Posterior Reversible Encephalopathy Syndrome (PRES) as dose limiting toxicity Minor reorganization of instructions within subsections to overall section Guidance on dose modification for PRES added along with explanatory text Guidance on minimum threshold for neutrophil count reduced to ≥1,000/μL	Update to align with known safety profile of niraparib Clarification of relevant safety instructions to minimize potential confusion Update to align with known safety profile of niraparib Update to align with revised safety monitoring guidance
Section 4.7.2. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic	New section added	Additional guidance to sites included in light of COVID-19
Section 6.2.3.1. Administration - Niraparib	Instruction for sequencing of dostarlimab infusion and niraparib administration	Additional clarity to investigative sites
Section 6.5. Dose Modification Appendix 9. mTPI-2 Design	Discussion of modified toxicity probability interval-2 (mTPI-2) design removed from section and moved to appendix	Better reorganization of the protocol to keep section limited to instruction on modification and separate statistical discussion
Section 6.7.1. Rescue Medications	Exception to allowable use of prophylactic cytokines added	Corrects discrepant information within protocol
Section 7.1. Discontinuation of Study Treatment	Reorganization of information within section Addition of instruction to discontinue both niraparib and dostarlimab if either treatment is to be discontinued Inclusion of additional guidance and supporting evidence for procedures for imaging assessments	Improved flow of information and additional guidance

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities Section 8.3.1. Time Period and Frequency for Collecting AE and SAE Information Section 8.3.5. Pregnancy	Revision of language for collection of information for SAEs and AEs Initial reporting requirement changed from 24 hours to 1 business day	Removal of discrepant information and improved clarity Revision to align with GSK standards
Section 8.3.6. Adverse Events of Special Interest	Pneumonitis and embryofoetal toxicity removed	Pneumonitis has been removed as the safety profile of niraparib has evolved Embryofoetal toxicity is captured in the Pregnancy section

Abbreviations: AE=adverse event; CCI [redacted]; CBC=complete blood count; COVID-19=Coronavirus disease 2019; DLT=dose-limiting toxicity; GSK= GlaxoSmithKline; mTPI-2=modified toxicity probability interval-2; PK=pharmacokinetic; PRES=Posterior Reversible Encephalopathy Syndrome; RP2D=recommended Phase 2 dose; SAE=serious adverse event.

Amendment 02 (23 November 2020)

Overall Rationale for the Amendment

Amendment 02 revises the protocol to include specific safety language noted during Health Authority review as detailed in Table 2.

Summary of Changes for the Amendment

Table 2: Summary of Changes for Amendment 02

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, Appendix 10. Protocol Amendment History (new), and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment and administrative information for prior amendment was moved to new Appendix 10. Protocol Amendment History. Editorial changes made throughout.	Editorial changes to align with the Sponsor's standard protocol template and ways of working, for conformity, clarity, flow, and typographical error correction, and for inclusion of specific language noted during Health Authority review

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Part 1A Design) Section 1.2. Schemas (Figure 1: Part 1A Study Schema, A. Dose Escalation) Section 4.1.1. Part 1A Design (including Figure 2: Part 1A Study Schema, A. Dose Escalation)	Clarified that Cohorts 1A and 1B might not be opened in parallel	To accurately reflect the study design
Section 1.1. Synopsis (Dose-Limiting Toxicity) Section 4.1.2.2. Dose-Limiting Toxicity	Clarified that a reason for a participant missing several doses of niraparib could be, but is not limited to, noncompliance Clarified that DLT criteria includes "any treatment-related" Grade≥2 uveitis, eye pain, or blurred vision, Grade ≥2 immune-related endocrine toxicity, and Grade 2 colitis or diarrhoea	Noncompliance is a possible reason that participants do not receive the intended exposure of niraparib These specific criteria should be deemed treatment-related to be considered a DLT
Section 1.1. Synopsis (Main Criteria for Inclusion) Section 5.1. Participant Inclusion Criteria	Clarified that participants must not be eligible for local curative treatment (criterion 1)	Participants who are eligible for local curative treatment are not permitted in the study
Section 1.1. Synopsis (Main Criteria for Exclusion) Section 5.2. Participant Exclusion Criteria	Added language for exclusion in cases of pregnant or breastfeeding participants (criterion 9) Modified that a participant should not have received a live vaccine within 30 days of starting study treatment (criterion 18) (changed from 14 days) Clarified that participants with QT interval prolongation >480 ms at screening are not eligible and no waivers are allowed (criterion 20)	Participants who are pregnant or breastfeeding are excluded from the study Participants must not receive live vaccines within 30 days of starting study treatment Participants with QT interval prolongation >480 ms at screening are not eligible for the study

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (General Study Conduct) Section 4.1.3. General Study Conduct Section 7.1. Discontinuation of Study treatment	Clarified that, during the long-term Follow-Up Assessment Period, follow-up might be conducted via a clinic visit or telephone contact	To accurately reflect study conduct
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities (footnote g) Section 8.2.7. Vital Signs, Height, and Weight	Clarified that blood pressure and heart rate monitoring which occurs weekly for the first 8 weeks during the Treatment Period is until/inclusive of Cycle 3 Week 2, not Cycle 3 Week 3	Error correction
Section 4.4. Dose Adjustment Criteria	Clarified that all treatment delays and discontinuations (ie, regardless of which study treatment) and reason should be recorded in the eCRF	To accurately reflect study conduct
Section 4.4.2. Dose Adjustment Criteria – Dostarlimab (Table 8: Guidelines for Treatment of Immune-Mediated Adverse Events of Interest) Section 6.7.1. Rescue Medications	Added guidelines for the management of myocarditis as a possible imAE when receiving dostarlimab	Added per Health Authority feedback
Section 5.3. Lifestyle Considerations	Added that participants should avoid exposure to ultraviolet light and take precautions when exposed to direct sunlight	Added due to the fact that photosensitivity has been reported for participants receiving niraparib
Section 6.7.2. Prohibited Medications	Updated guidance regarding concomitant therapies used while receiving niraparib and dostarlimab	Updated per Health Authority feedback and to align with current product labels

Abbreviations: COVID-19-Coronavirus Disease 2019; DLT=dose-limiting toxicity; eCRF=electronic case report form; imAE=immune-mediated adverse event; PRES=Posterior Reversible Encephalopathy Syndrome; UK=United Kingdom.

Amendment 03 (20 July 2022)

Overall Rationale for Amendment 03:

- To update safety guidance, particularly with respect to MDS/AML information.
- To include new appendix for International Neuroblastoma Response Criteria (INRC).

- To add benefit risk assessment section based on clinical studies of niraparib and dostarlimab.
- CCI [redacted].
- To update inclusion and exclusion criteria.
- To increase clarity and/or remove discrepancies.

All changes are listed in Table 2.

Table 2: Summary of Changes for Amendment 03

Section(s) Affected	Description of Change	Brief Rationale
Headers, title page, Protocol Amendment Summary of Changes, Appendix 12. Protocol Amendment History, and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment and administrative information for prior amendment was moved to Appendix 12. Protocol Amendment History. Editorial changes made throughout.	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Title page	Updated compound number "GSK4057190 to GSK4057190A"	To present current correct compound number for dostarlimab
Section 1.1 Synopsis (Secondary objectives) Section 3 Study Objectives and Endpoints	Added new secondary objective; to assess the immunogenicity of dostarlimab in paediatric participants	To correct lack of secondary objective given immunogenicity analyses are described in the protocol and an immunogenicity population is defined in Section 9 Statistical Considerations
Section 1.1. Synopsis (Part 1 Dose Escalation Design) Section 4.1 Part 1 Dose Escalation Design	Added "DLT-evaluable" in advance of required numbers of cohort participants	To clarify that dose escalation (or not) decisions are to be made based on data only from participants who have been determined to be DLT-evaluable per protocol definition.
CCI [redacted]		

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 1.1 Synopsis (Part 1A Design) Section 4.1.1: Part 1A Design	Included language supporting use of 100 mg niraparib in participants ≥50 kg	To provide justification based on results from Study NOVA for selection of 100 mg niraparib dose in participants ≥50 kg in size with an option for intra-participant dose escalation.
Section 1.1. Synopsis (Dose Limiting Toxicity) Section 4.3 Dose Limiting Toxicity	Added statement indicating "participant may continue on study treatment following a DLT" Replaced "8" with "9" in phrase "missed 8 or more doses"	To clarify that study treatment is not required to be discontinued following a DLT. To correct error in statement. Participant must miss 9 or more doses of niraparib to have a dosing compliance value <80% over the 42-day DLT observation interval.
Section 1.1. Synopsis (Dose Limiting Toxicity) Section 4.3 Dose Limiting Toxicity	Added new DLT: any treatment-related toxicity resulting in reduction (for niraparib) or interruption of study treatment such that overall patient dosing is less than that required for DLT evaluability.	To acknowledge role of treatment-related toxicities in overall determination of treatment safety.
Section 1.1. Synopsis (General Study Conduct) Section 4.4 General Study Conduct Section 1.3. Schedule of Activities (Table 3 Footnote c) Section 7.1 Discontinuation of Study Treatment	Clarified long-term follow-up assessment period 90 (±14) days "after the last dose of study treatment"	To clearly define specific starting point from which to initiate long-term follow-up safety assessments

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (General Study Conduct) Section 4.4 General Study Conduct	Added details for required imaging schedule for the period post-12 months after first dose of study drug	To present a reduced scan schedule for participant monitoring that reduces overall radiation exposure and begins 12 months after the first dose of study drug.
Section 1.1. Synopsis (General Study Conduct) Section 1.3. Schedule of Activities (Table 3 Footnote v) Section 4.4 General Study Conduct Section 8.3.1. Time Period and Frequency for Collecting AE and SAE Information	Updated details on collection of AEs "or to a minimum of 30 days after the last dose of study treatment if the participant starts subsequent anticancer treatment"	To more clearly describe interval during which AE information is to be collected in the event of initiation of additional anticancer treatment.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 1) Section 1.3: Schedule of Activities Table 3 Footnote e Section 5.1. Participant Inclusion Criteria (criterion 1)	• Reorganized content of criterion • CCI [redacted] • Replaced "prior to enrolment" with "prior to Cycle 1 Day 1"	CCI [redacted]
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 1) Section 5.1. Participant Inclusion Criteria (criterion 1)	Moved "and must not be eligible for local curative treatment" from requirements for participants with tumours other than the specific tumours identified to refer to all participants.	To correctly describe the overall participant population that is eligible for study enrolment.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 3) Section 5.1. Participant Inclusion Criteria (criterion 3)	Added Inclusion Criterion 3 stating requirement for measurable/evaluable disease by tumour type at time of study enrolment.	To include a criterion needed to support enrolment of participants who could be followed for response to study treatment.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 6) Section 5.1. Participant Inclusion Criteria (criterion 6)	Updated note describing timing for collection of blood sample for complete blood count	To better describe a correct and more reasonable washout period for support agents (transfusion, colony-stimulating factors, erythropoietin) received prior to collection of blood for complete blood count during screening.
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 8) Section 5.2: Participant Exclusion Criteria (criterion 8)	Removed bullets on blood transfusion and growth factors in exclusion criteria 8	To remove the guidance for permitted timing for transfusions and colony-stimulating factor administration as this guidance has been updated in Inclusion criterion 6.
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 13) Section 5.2: Participant Exclusion Criteria (criterion 13)	Replaced Exclusion Criterion 13 with: Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.	To update exclusion criteria to include additional criterion to support participant safety.
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 14) Section 5.2: Participant Exclusion Criteria (criterion 14)	Updated exclusion criteria 14 to clarify guidance on hematologic side effects from prior anticancer therapy.	To clarify information on excluded cytopenia occurrence and duration
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 16) Section 5.2: Participant Exclusion Criteria (criterion 16)	Added new exclusion criteria “Toxicity related to prior immunotherapy that led to study treatment discontinuation.”	To include guidance for enrolment of patients who had previously experienced toxicity in response to immunotherapy and to align eligibility requirements with those of dostarlimab protocols in general.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 17) Section 5.2: Participant Exclusion Criteria (criterion 13) Section 5.2: Participant Exclusion Criteria (criterion 17)	Deleted exclusion criterion 13. Updated exclusion criterion 17 to clarify permitted window relative to first dose of study treatment for prior systemic anticancer therapy. Combined text from exclusion criterion 13 with text in exclusion criterion 17.	To update permitted window for receipt of prior anticancer therapy from "within 3 weeks" prior to first dose of study treatment to "within 3 weeks or 5 half-lives, whichever is shorter" - a change which was made in response to an investigator's suggestion, and which reflects half-life data for most common standard of care therapies enrolled patients with the specified tumour types. In addition, to make the excluded window consistent for investigational agents or devices and for approved systemic therapies of all types.
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 21) Section 5.2: Participant Exclusion Criteria (criterion 21)	Updated exclusion criterion 21 with corrected QTc values	To align excluded QTc values with values appropriate for participants to be treated with dostarlimab.
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 22) Section 5.2: Participant Exclusion Criteria (criterion 22)	Added exclusion criteria 22 to clarify that solid organ transplant is not permitted.	To prohibit enrolment of participants who are receiving immunosuppressive therapy that might impact effectiveness of dostarlimab as a PD-1 inhibitor.

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 1.1. Synopsis (Criteria for Evaluation: Safety)	Added “AEs” in safety evaluation	In line with study level requirements
CCI [redacted]		

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 1.3. Schedule of Activities (Table 3)	Added "Post Treatment" to column header for FUP assessment Period	To align column header content with text clarifying that Follow-up visits were to occur every 90 days following end of study treatment.
Section 1.3 Table 3 Schedule of Activities	Removed -10-day window from Screening period	To correct outside limit of Screening activities window to -28 days rather than -28 days + 10 additional days.
Section 1.3 Table 3 Schedule of Activities	Merged cells for EOT Visit, Safety FUP Visit, and FUP Assessment Period for the rows for several disease assessment activities	To clarify that measures of disease assessment are to continue throughout the EOT and follow-up period if appropriate.
Section 1.3. Schedule of Activities (Table 3 and Footnote j)	Addition of pregnancy testing for WOCBP at End of Treatment and 30-day Safety Follow-up Visits	To ensure pregnancy did not occur during the excluded period.
Section 1.3. Schedule of Activities (Table 3 and Footnote l) Section 8.2.8 Electrocardiogram	Addition of 12-lead ECG testing added in Cycle 3	In line with study level requirements
Section 1.1 Synopsis, Section 1.3 Schedule of Activities (Table 3 and Footnote q, r) Section 8.1.2.1.1 Timing and Considerations for Radiologic Assessments	Added text indicating that tumour assessments should be conducted every 9 weeks (every 63 [±7] days) from the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter.	To reduce total number of scans conducted throughout duration of participant enrolment and thereby reduce radiation exposure overall.
Section 1.3. Schedule of Activities (Table 3 Footnote b)	Added additional details on safety FUP visit	To clarify the Safety FUP visit window

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Table 3 Schedule of Activities Footnote k Section 8.2.13 Viral Disease Testing CCI [redacted]	• Replaced "will' with "must" in the phrase "Testing for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, and HIV must be conducted where required by local Regulations or if warranted by participant's history in accordance with Table 3. • CCI [redacted]	To strength the guidance for viral disease testing during screening. CCI [redacted]
Section 1.3 Schedule of Activities (Table 3 Footnote m) Section 8.1.2.1.1 Timing and Considerations for Radiologic Assessments	Removed the language that "MRI should only be used if clinically appropriate, when CT is contraindicated, and preferably for imaging of the brain"	To remove restrictions to use of MRI in medically appropriate scanning situations
Section 1.3. Schedule of Activities (Table 3 Footnote i) Section 8.2.12: Laboratory Assessments	Updated to replace baseline with "Cycle 1 Day 1" and to clarify guidance for Cycle 1 Day 1 sample collection.	To clarify that if the screening laboratory samples were collected within 7 days of Cycle 1 Day 1, then collection of these samples did not need to be repeated for Cycle 1 Day 1.
Section 1.3. Schedule of Activities (Table 3 Footnote w, x and z)	Updated information for dostarlimab PK, ADA, neutralising antibodies, and biomarker sample collection	To provide additional guidance for procedures and timing of dostarlimab PK, ADA, neutralising antibodies, and biomarker sampling.
Section 2.1.1. Clinical Data	Updated the background on Niraparib marketing application status	To describe that niraparib has been approved as maintenance treatment for patients with advanced or recurrent gynaecologic cancers.

Section(s) Affected	Description of Change	Brief Rationale
Section 2.2.1. Clinical Data	Updated the background on Dostarlimab marketing application status	To describe that dostarlimab is approved for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer.
Section 2.6 Benefits and Risks Assessment	Substantial new sections added summarizing the overall benefit/risk of the study	To align protocol structure with that of GSK standard protocol template and to incorporate risk/benefit language to meet protocol content requirements as outlined in GCP E6(R2) (EMA / CHMP / ICH /135 /1995) sections 6.2.3. and 6.2.4.).
Section 3 Study Objectives and Endpoints	Revised PK endpoint	To describe the parameters constituting the endpoint measures.
CCI [redacted]		
Section 4. Overall design	Transferred paragraph on review of safety and PK data from Section 8.4 Pharmacokinetics, Immunogenicity and Biomarkers	To provide clarity on process for review of safety and PK data and role in RP2D determination
CCI [redacted]		

Section(s) Affected	Description of Change	Brief Rationale
Section 4.7.1 Niraparib; Table 11 (Niraparib Dose Modifications for Haematologic Adverse Reactions)	Added MDS/AML language	To describe laboratory assessments that must be conducted if MDS/AML is suspected
CCI [redacted]		CCI [redacted]
	• Added "unless a discussion with the Sponsor's Medical Monitor has occurred" added to statement about niraparib dose-re-escalation following a dose reduction." • Updated required neutrophil count recovery level from 1000/µL to 1500/µL.	To clarify conditions under which niraparib dose may be re-escalated following dose reduction. To align dose modification guidance for neutropenia with that in niraparib United States prescribing information (March 2021).
Section 4.7.2 Dose Adjustment Criteria for Dostarlimab and Section 6.7.1 Rescue Medication	• Transferred text details on guidance by type of immune-related AE from Section 6.7.1 Rescue Medication to Table 12: Guideline for treatment of Immune-Related Adverse Events • Table 12 updated • Changed the term "adverse reaction" to "adverse event" • Added guidance (text and Table 13) for infusion reactions.	To combine management guidance for immune-related AEs in one location – Table 12. Table 12 was updated in multiple areas to reflect most up-to-date guidance for management of AE accompanying treatment with dostarlimab. To provide appropriate guidance for management of reactions associated with dostarlimab infusion.
CCI [redacted]		
Section 6.2.3.2 Dostarlimab	Added text describing recommended post-infusion observation period for dostarlimab infusion.	To provide additional guidance for participant safety monitoring following infusion of dostarlimab

Section(s) Affected	Description of Change	Brief Rationale
Section 6.4 Study Treatment Compliance	Additional content added on dosing diary	To clarify completion of dosing diary is mandatory for the first two cycles and to align protocol content with that in the study pharmacy manual
Section 7.1. Discontinuation of Study Treatment	Removed the option for participants to continue treatment beyond confirmed disease progression, and added the requirement to discuss with participant's legal guardian treatment beyond radiological evidence of disease progression (prior to confirmed disease progression) Addition of reasons for discontinuing treatment: •MDS/AML (as confirmed by a hematologist) •Secondary malignancies other than MDS/AML may require discontinuation to be assessed by the treating physician in agreement with the Sponsor. •Hypertensive crisis / PRES	To clarify that treatment beyond confirmed disease progression is not permitted. To provide additional reasons based on new safety data that would require treatment discontinuation.
Section 7.1.1 Liver Chemistry Stopping Criteria Appendix 8 Liver Safety: Required Actions and Follow-up Assessments Appendix 9 Liver Safety Drug Restart or Rechallenge Guidelines	Updated text throughout each noted section/appendix	To align guidance in this protocol amendment with GSK standards for liver events in oncology trials
Section 7.1.2 QTc Stopping Criteria	Added new section on QTc stopping criteria	To align with safety monitoring requirements for dostarlimab
Section 8.1.2.1.1 Timing and Considerations for Radiologic Assessments	Added text permitting collection of participant scan data	To permit – per protocol – the collection of participant scan data under specific circumstances such as investigation of a significant safety event

Section(s) Affected	Description of Change	Brief Rationale
Section 8.1.2.2. Bone Marrow Assessments	Added text describing timing of bone marrow assessment post-baseline if participant's bone marrow was positive for disease at baseline.	To align text in Section 8.1.2.2 with that in Section 1.3, Table 3 Schedule of Activities for bone marrow assessment
CCI [redacted]		
Section 8.2.12 Laboratory Assessments	• Replaced Baseline with Cycle 1 Day 1 • Added guidance about timing of laboratory assessments at screening and Cycle 1 Day 1. • Added MDS/AML safety language • Formatted as table all measured lab parameters	To adopt a more precise term than "Baseline" To clarify that Cycle 1 Day 1 laboratory samples did not need to be collected if collected for Screening less than 7 days prior To describe laboratory assessments that must be conducted if MDS/AML is suspected Reformatted list of laboratory parameters for easier reading

Section(s) Affected	Description of Change	Brief Rationale
Section 8.4 Pharmacokinetics, Immunogenicity and Biomarkers Section 8.4.1 PK Sample Collection Section 8.4.2 Immunogenicity Sample Collection	• PK, Immunogenicity, Exploratory sample collection Sections moved from Section 8.1.2 Secondary Efficacy Endpoints to Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	To combine in one section all study procedures related to PK, immunogenicity, and biomarker sample collection and intent for analysis. Descriptive statements about statistical analyses of data from the results of these procedures were moved to Section 9 Statistical Considerations
CCI [redacted]		CCI [redacted]
CCI [redacted]		
Section 8.4.2 Immunogenicity Sample Collection Section 9.3.3.5. Immunogenicity Analysis	Added content “The number and percentage of participants who become positive for ADAs and who develop neutralising antibodies will be summarized”	To reflect the latest information regarding ADA Endpoint
Section 9.3.3.2 Safety Analyses	Added new content “(90 days for SAEs)”, “for both AEs and SAEs”, and replaced word “subsequent” with “new”	To reflect the latest information regarding safety analyses
CCI [redacted]		

Section(s) Affected	Description of Change	Brief Rationale
Appendix 1 – Committees Structure	Updated information for establishment and composition of an independent data oversight committee	To clarify that a committee that is independent of all aspects of the study and that is dedicated to oversight of safety and efficacy data from participants in Part 2 will be established. To clarify that details of committee composition and function will be described in a formal charter.
Appendix 1 – Dissemination of Clinical Study Data	Removed redundant text: GSK intends to make anonymised participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding	To remove text that was redundant with text already present in this section.
Appendix 2 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting – Definition of an Adverse Event of Special Interest	Deletion of AE “pneumonitis” and “embryo-fetal toxicity” from definition of Niraparib AESIs	Updated to reflect the latest information regarding definition of Niraparib AESIs
Appendix 5. Guidelines for Assessment of Disease, Disease Progression and Response Criteria in Participants with Neuroblastoma – Adapted From Revised International Neuroblastoma Response Criteria (INRC)	Added new INRC Appendix	Included to provide necessary and supportive guidance to sites carrying out disease assessments for participants with neuroblastoma.
CCI [redacted]		

Amendment 04 (12 Dec 2024)

Overall Rationale for Amendment 04:

Amendment 04 is a substantial global amendment resulting in changes in participant dosing regimen(s) based on emerging data and safety information. Administrative, editorial, and clarifications for study conduct are also included.

A general description and brief rationale(s) for key changes are provided in Table 2 below. The synopsis was also updated to align with the changes in the protocol body, where applicable.

Table 2 Summary of Changes for Amendment 04

Section(s) Affected	Description of Change	Brief Rationale
Headers, Title Page, abbreviations, Protocol Amendment Summary of Changes, List of Abbreviations, Appendices, References, and throughout Section 6 Study Treatments and Concomitant Therapy Section 6.2.5 Study Treatment Handling and Disposal Section 8.2.2 Demographic/Medical History Section 8.3.2 Method of Detecting AEs and SAEs Section 8.3.4 Regulatory Reporting Requirements for SAEs	Headers and title page updated with new document numbers, dates, and amendment information; Protocol Amendment Summary of Changes section was updated to include details and rationales for this amendment; editorial revisions for consistency with Sponsor's ways of working, minor corrections and formatting adjustments, and to add clarification and/or remove discrepancies	Editorial changes to align with the Sponsor's standard protocol template, style guide, and ways of working and for accuracy, clarity, conformity, flow, and typographical error correction.
Throughout	CCI [redacted]	CCI [redacted]
Section 1.2 Schemas, Figure 1 Section 2.6.3.1 Niraparib Dosing Section 2.6.3.2 Dostarlimab dose Table 8 Objectives and Endpoints for Study 213406 Section 4 Overall Design Section 4.1.1	• New Figure 1 outlining overall study schema and Part 1B study schema (new Figure 5); updated figure numbering throughout CCI [redacted]	

Section(s) Affected	Description of Change	Brief Rationale
Section 4.1.2 Part 1B Design Figure 5 Part 1B Study Schema Under Protocol Amendment 04 Section 4.2 Intra-participant Dose Escalation Section 4.4 General Study Conduct Section 4.5 Number of Participants Section 4.6 Treatment Assignment Section 4.7 Dose Adjustment Criteria. Section 5.1 Participant Inclusion Criteria Section 6.1 Study Treatments Administered Section 6.2.1 Study Treatment Packaging and Labelling Section 6.2.3.1 Niraparib Section 6.2.3.2 Dostarlimab Section 6.4 Study Treatment Compliance Section 9 Statistical Considerations Section 9.1 Sample Size Determination Appendix 13 Part 1B Cohort A Niraparib Dose Reduction Recommendations for AEs	CCI [redacted] • Part 2 primary objective text adjusted to include safety and tolerability to reflect updated objectives of Safety Run-in outlined in supplements A and B • Update overall design to reflect updated dosing, updated details for completed portions of the study, and mention of Safety Run-in for Part 2, where applicable • Minor changes to Part 1A study design to reflect study pause in enrolment and results from data collected • CCI [redacted] • Included details for treatment assignment for those participants that turn 18 years of age while on study expected to stay on TfOS niraparib formulation • New section added describing dose adjustments and criteria for adjustments due to changes in age and weight, along with subsections heading for AEs • Inclusion Criterion #2 updated to outline age enrolment requirements under Amendment 04 • CCI [redacted] • Number of participants updated to include actual numbers of participants enrolled to date and planned enrolment numbers under Amendment 04 with updated study design cohort; includes minor update to planned cohorts for Part 1B under Protocol Amendment 04 • CCI [redacted]	CCI [redacted]

Section(s) Affected	Description of Change	Brief Rationale
	• New dose reduction table for haematological AEs for Part 1B Cohort A based on the revised dosing regimen	
Section 4.7.2.1 Niraparib Table 9: Niraparib Dose modifications for Nonhematologic Adverse Reaction Table 10: Niraparib dose modification for haematologic adverse reaction	• Updated to include details on number of permitted dose reductions • Updates to requirements for dose modification details for haematological and non-haematological events	Updated to align with safety management requirements for niraparib.
Section 4.7.2 Dose Adjustment for Adverse Events Section 4.7.2.2 Dostarlimab Table 11: Guidelines for Treatment of Immune-Related Adverse Events	• Updated details for dose adjustments for dostarlimab due to AEs including table outlining guidelines for treatment of imAEs	Updated to align with safety management requirements for dostarlimab.
Section 2.6.1.1 Niraparib Monotherapy	• Table 5 Summary of Risks and Mitigations for Niraparib updated	To align with current important identified and potential risks for niraparib as defined in the EU RMP
Section 2.6.1.2 Dostarlimab monotherapy	• Table 6 Summary of Risks and Mitigations for Dostarlimab updated	To align with current important identified and potentials risks for dostarlimab as defined in the EU RMP
Section 3, Table 8 Objectives and Endpoints for Study 213406 Section 9.3.4 Exploratory Endpoints	CCI [redacted]	
Section 5.1 Participant Inclusion Criteria	• Inclusion Criterion #6: organ function parameters updated for haemoglobin	To align with the patient population
Section 1.3 Schedule of Assessments (Table 3 footnote) Section 4.4 General Study Conduct Section 5.1 Inclusion Criteria (Criterion 7c) Section 8.2.9 Pregnancy Testing	• Clarification included that WOCBP must have a pregnancy test even if they had received treatment that potentially but not definitely would prohibit becoming pregnant • Timeline for providing negative pregnancy test result updated to 24 hours	Updated to increase assurance that female participant of childbearing potential is not pregnant as close as possible to time of study drug dosing.
Section 5.2 Participant Exclusion Criteria	• Exclusion Criterion #5 – Clarification participants with previously treated CNS metastases for evidence of disease progression	Updated text to provide more accurate description of changes indicative of progression of disease in brain.
Section 5.2. Participant Exclusion Criteria Appendix 12 Consideration for	• Exclusion Criterion 12 – updated wording regarding HbsAg/HbcAB for HBV screening • New Appendix 12 added for guidance surrounding HBV testing	To permit the inclusion of patients with past HBV infection.

Section(s) Affected	Description of Change	Brief Rationale
Participants with Past HBV Infection		
Section 5.2. Participant Exclusion Criteria	• New exclusion criteria 23 and 24 added regarding HCV testing	To align with current protocol template language.
Section 5.2. Participant Exclusion Criteria	• Exclusion criterion #9 – updated language regarding when breastfeeding can resume	To align with guidance in current US prescribing information for niraparib and dostarlimab.
Section 5.2. Participant Exclusion Criteria	• Exclusion criterion #15 – updated language regarding AEs in participants undergoing systemic anticancer therapy with exceptions as agreed with Sponsor.	Expansion of text to more clearly define conditions for participant eligibility.
Section 7.1.1 Liver Chemistry Stopping Criteria Appendix 8 Liver Safety: Required Actions, Monitoring, and Follow-Up to Assess Causality of Liver Event	• Figure updated • Liver monitoring details updated in the Appendix	Updated for patient safety in alignment with Sponsor template.
Section 4.4 General Study Conduct Section 7.1 Discontinuation of Study Treatment Section 7.2 Withdrawal of Consent Section 7.3 Participant Discontinuation/ Withdrawal from the Clinical Study	• Text adjusted to clarify discontinuation reasons and requirements should alternative anticancer therapy be started, including expectations for Safety FU period • Text added acknowledging if in-person visits are not possible • Text added regarding data collection from public domains following withdrawal of consent • Additional updates to align wording and align with Sponsor template and EU CTR requirements	Clarification for study conduct and to align with Sponsor template and the program.
Section 1.3 Schedule of Assessments (including footnote) Section 4.7.1 Dose Adjustment for Age and Weight	• CBC with differentials assessments updated to include twice weekly collection in Cycles 1 and 2, and after a niraparib dose increased due to a birthday or weight change; including footnote updates	To permit more frequent monitoring of haematology values (particularly for platelets) to permit early rapid detection of onset of thrombocytopenia over the first 2 cycles of treatment and additional safety monitoring in response to an increase in niraparib dose and to allow use of testing at facilities outside the research clinic.
Section 4.8 End of Study Definition Section 6.7 Continued Access to Study Intervention After the End of the Study	• Updated wording in end of study definition	Clarification for study conduct
Section 5.1. Participant Inclusion Criteria	• Criterion #1: replaced statement '***local curative treatment***.' with '***alternative curative treatment***.'	Clarification

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (including footnote) Section 4.4 General Study Conduct Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	CCI [redacted]	Clarification for study conduct and alignment with Sponsor requirements for sample storage
Section 1.3. Schedule of Activities (including footnote) Section 8.2.7. Vital Signs, Height, and Weight	• Updated timing for collection of vital signs, height, and weight measurements including during follow-up period and clarifications for measuring height and weight.	Clarification for study conduct to permit consistent monitoring of vital signs throughout the Treatment Period.
Section 2.1.1 Clinical Data for Niraparib Section 2.2.1 Clinical Data for Dostarlimab Section 2.3 Rationale for Synergy Between PARP Inhibitors and Immune Checkpoint Inhibitors Section 2.6.1.3 Niraparib and Dostarlimab Combination Safety and Efficacy	• Update regulatory, clinical, and safety information and added references to IBs	Editorial updates to align with current information for the investigation products.
Section 1.3 Schedule of Activities (Table 3, footnote) Table 4 Tumour Assessment Flowchart Section 4.4 General Study Conduct Section 8.1.2.1 Radiological Assessment	• Clarification that brain scans must include IV contrast and brain scan by MRI preferred to that by CT including in table footnote and Table 4 outlining tumour assessments • Clarifications in imaging requirements for participants at time of study treatment discontinuation • Added statement regarding follow-up disease assessments for participants with CR or PR while on treatment, who discontinue • Addition of Schwartz, 2016 reference for RECIST	Clarification for study conduct.
Section 1.3 Schedule or Assessments (footnote) Section 8.2 Assessment of Safety Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	• Detail included regarding prioritisation of blood sample collection in the event of concerns for excessive blood volume withdrawal	Clarification for study conduct to provide guidance to sites on relative importance of collection of specific blood samples.
CCI [redacted]		

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 1.3 Schedule of Assessments (including footnotes) Table 4: Tumour Assessment Flowchart Section 4.4 General Study Conduct Section 8.1.2.1 Radiological Assessments Appendix 4 Guidelines for Assessment of Disease, Disease Progression, and response Criteria – Adapted from RECIST Appendix 5 Guidelines for Assessment of Disease, Disease Progression and Response Criteria in Participants with Neuroblastoma – Adapted from Revised International Neuroblastoma Response Criteria (INRC)	• Adjusted wording in Table 3 and Table 4 surrounding tumour assessments for clarification and align discontinuation wording • Guidelines for Assessments using RECIST updated to align with guidelines to include definitions of non-target and target lesions for evaluation and removal of best overall response information • Schwartz, 2016 reference included for RECIST • Minor updates in INRC guidelines Table 23 regarding tumour response at metastatic soft tissue and bone sites PD definition	Updates to ensure key imaging assessments conducted appropriately and consistently. Clarifications of standard disease assessment criteria. Best overall response details removed as this is determined programmatically by Sponsor.
Section 1.3 Schedule of Assessments (including footnote) Section 8.4.3 Exploratory biomarkers	• CCI [redacted]	Clarification.
Section 4.4 General Study Conduct Section 8.3.1 Time Period and Frequency of Collecting AE/SAE Information Section 8.3.3 Follow-up of SAEs	• Adjusted wording surrounding collection and follow-up of nonserious AEs, and expectations for follow-up of SAEs during long-term follow-up period and when starting alternative anticancer therapy.	Clarification for study conduct.
Section 6.7 Continued Access to Study Treatment	• Section added per protocol template to clarify intended access to treatment for participants in the study following completion.	Clarification for study conduct and alignment with Sponsor template.
Section 7.1.2 QTc Stopping Criteria	• Adjusted wording regarding ECG reading requirements	To align text with standard program language.
Section 8.2.12 Laboratory assessments Table 15: Safety Laboratory Assessments	• Note included regarding baseline platelet count of 100 000/uL in this study • Added reference to table of tests to be performed, AESI term updated, text added to clarify handling of clinically significant values and AE reporting per Sponsor template • Footnote added to Table 15 regarding values to be recorded (either absolute counts or percentages) for differential values	Clarifications included rationale for baseline platelet count, for study conduct, and to align with Sponsor template.

Section(s) Affected	Description of Change	Brief Rationale
Section 8.2.1 Safety Parameters Appendix 2 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	• Urinalysis wording updated to clarify urinalysis is not being conducted regularly, but only under certain circumstances	Clarification for study conduct
Section 8.2.3 Disease History	• Removed 'for participants with neuroblastoma only' from stage of initial diagnosis collection • Deleted collection of 'previously treated but currently stable CNS metastases'	Clarification for study conduct to not limit data collection for initial diagnosis data collection and aligned collection regarding CNS disease with data collection per CRFs.
Section 8.3.5. Pregnancy	• Deleted statements related to female participant becoming pregnant during the study and continuation of treatment. Additional clarifications added regarding sharing pregnancy information.	For consistency with Section 7.1 and Sponsor template.
Section 8.3.6 AESI	• Updated term relating to second primary malignancies and added statement that there are no AESIs for dostarlimab • Clarifying language added surrounding AESI collection timing.	Clarification to align with current safety information and text within protocol.
Section 8.5 Genetics	• CCI [redacted]	Clarification.
Appendix 1 Regulatory, Ethical, and Study Consideration	• Added additional information under recruitment strategy, data protection, dissemination of clinical study data, data quality assurance, source documents and study/site termination, and publication policy	To align with EU CTR requirements and Sponsor template.
Appendix 2: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	• Included TEAE definition, severity grades for intensity, updated information on assessment of causality with more than 1 intervention, outcome assessment options added, and detail included regarding AE/SAE/pregnancy follow-up	Clarification for study conduct/reporting and to align with Sponsor template.
Appendix 3 contraception guidelines	• Updated definitions for WOCBP	To align with updated Sponsor definition.

Abbreviations: CCI [redacted]; ADA=antidrug antibody(ies); AE=adverse event; AESI=AE of special interest; CBC=complete blood count; CNS=central nervous system; CR=complete response; CRF=case report form; CT=computed tomography; CTCAE=common terminology criteria for Adverse Events; CTR=Clinical Trials Regulations; EU=European Union; ; FU=follow-up; HbcAB=hepatitis B core antibody, HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV=hepatitis C virus; IB=investigator's brochure; INRC=International Neuroblastoma Response Criteria; imAE=immune-mediated AE; MRI=magnetic resonance imaging; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; RMP=risk management plan; SAE=serious AE; SoA=schedule of assessments; TEAE=treatment-emergent AE: TfOS=tablet for oral suspension; WOCBP=woman of childbearing potential.

Amendment 04 GBR-1 (08 Aug 2024)

Overall Rationale for Amendment 04 GBR-1:

Amendment 04 GBR-1 is a UK-specific amendment addressing agency feedback regarding exclusion criterion 15. A description and rationale for the changes is provided in Table 2 below.

Table 2: Summary of Changes for Amendment 04 GBR-1

Section(s) Affected	**Description of Change** (~~deleted text~~; **added** text)	**Brief Rationale**
Headers, Title Page, Protocol Amendment Summary of Changes, Appendix 11 Country-specific Requirements	Headers and title page updated with new document amendment number/approval date, and amendment information; Protocol Amendment Summary of Changes section was updated to include details and rationale for this amendment; country-specific appendix for global amendments removed (remaining appendices renumbered) and associated text in protocol sections/tables adjusted.	Editorial changes to align with the Sponsor's standard protocol template, style guide, and ways of working.
Synopsis Section 5.2 Participant Exclusion Criteria	Exclusion criterion #15 updated as follows: Participant has not recovered (i.e., to Grade ≤1 or to baseline) from systemic anticancer therapy-induced AEs. Note: Participants with ~~certain AEs that are considered either nonclinically significant or are deemed stable or irreversible are exceptions to this criterion and may qualify for the study after discussion with the GSK Medical Monitor. Examples of AEs include, but are not limited to, alopecia,~~ hearing impairment, **alopecia**, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/**or** Grade ≤2 neutropenia **are an exception to this criterion and may qualify for the study.**	Regulatory agency feedback.

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TITLE PAGE

SUPPLEMENT A

PROTOCOL 213406

PART 2: OSTEOSARCOMA EXPANSION COHORT

Protocol Title:	A PHASE 1, MULTICENTRE, OPEN-LABEL, DOSE ESCALATION AND COHORT EXPANSION STUDY OF NIRAPARIB AND DOSTARLIMAB IN PAEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMOURS
Protocol Number:	213406 Amendment 05
Compound Number or Name:	Niraparib (GSK3985771), Dostarlimab (GSK4057190A)
Brief Title:	Dose Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Participants with Solid Tumours
Study Phase:	Phase 1
Sponsor Name and Legal Registered Address:	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Medical Monitor Name and Contact Information:	Contact Information can be found in the local study contact information
Sponsor Signatory:	Nidale Tarek, MD Senior Medical Director GSK
Regulatory Agency Identifying Number(s):	EudraCT Number: 2020-002359-39 EU CT: 2024-511071-16
Approval Date:	17 Dec 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date
Amendment 05	17 Dec 2024
Amendment 04 GBR-1	08 Aug 2024
Amendment 04	23 May 2024
Amendment 03	20 July 2022
Amendment 02	23 November 2020
Amendment 01	16 October 2020
Original Protocol	12 May 2020

Amendment 05 (17 Dec 2024)

Overall rationale for the current Amendment:

Protocol Amendment 05 is a substantial amendment that aligns Protocol Amendment 04 with all aspects of the UK-specific Protocol Amendment 04 GBR-1, resulting in a single global amendment. Additional changes include an update of the sponsor's legal registered address plus administrative and editorial updates and clarifications for study conduct.

A general description and brief rationale(s) for key changes are provided in Table 2 below. The synopsis was also updated to align with the changes in the protocol body, where applicable.

Table 2 List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Title Page	Sponsor legal address update	To align with current GSK policy
Section 1.1 Synopsis Methodology] Section 4.1 Overall Study Design	Language updated to indicate that the dose escalation committee (DEC) will review safety data and will determine future enrollment plan	To more clearly describe the role of the DEC in safety data review process overall
Section 1.1 Synopsis Main Criteria for Inclusion; Section 5.1 Participant Inclusion Criteria Point 03	Addition of relevant time point ("at screening")	To clearly indicate at what point in the study disease characteristics were to be evaluated
Section 1.1 Synopsis Main Criteria for Exclusion; Section 5.2 Participant Exclusion Criteria Point 17	Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic anticancer therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.	To revert the wording to that in Protocol Amendment 04, which provided more specific criteria for enrollment of participants with ongoing toxicities.

Section # and title	Description of change	Brief rationale
CCI [redacted]		
Section 1.3 Schedule of Activities (SoA) Footnote x	"Cycle 1 Day 1 2.5 hour samples must be collected at the scheduled time ±0.5 hour" was added	To more specifically define the permitted sample collection window
Section 1.1 Synopsis Objectives Section 3 STUDY OBJECTIVES AND PURPOSE Table 5	Text was added to Part 2 Safety Run-in Secondary Objective for general standard safety objective	To ensure that all safety data were assessed in Part 2 Safety Run-in not just DLTs and events of Grade ≥3 thrombocytopenia
CCI [redacted]		
Throughout document	Minor corrections and formatting adjustments were made	To add clarification and increase readability

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: GSK	
Name of Investigational Product: Niraparib, dostarlimab	
Name of Active Ingredient: Niraparib, dostarlimab	
Title of Study: A Phase 1, Multicentre, Open-label, Dose escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients with Recurrent or Refractory Solid Tumours **Part 2: Osteosarcoma Expansion Cohort**	
Study Centre(s): Multicentre	
CCI [redacted]	**Phase of Development:** Phase 1

Objectives:

The following are the objectives for the Safety Run-in Cohort and Osteosarcoma Expansion Cohort of this study.

Part 2 Safety Run-in

Primary:

The primary objective of this cohort is as follows:

- to assess the safety and tolerability of the CCI [redacted] by assessing dose limiting toxicity (DLT) and Grade ≥3 thrombocytopenia adverse events (AEs) in paediatric participants

Secondary:

The secondary objectives of this cohort are as follows:

- to evaluate additional measures of anticancer activity, including objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) in paediatric participants
- to characterise the pharmacokinetics (PK) of niraparib in paediatric participants
- to evaluate the safety of the combination o CCI [redacted] in paediatric participants

Part 2 Expansion

Primary:

The primary objective of this cohort is as follows:

- to assess the antitumour activity of the combination of niraparib and dostarlimab, assessed primarily by the PFS rate at 6 months (PFS6) (using Response Evaluation Criteria in Solid Tumours [RECIST] v1.1 criteria) in paediatric participants.

Secondary:

The secondary objectives of this cohort are as follows:

- to evaluate additional measures of anticancer activity, including ORR, DOR, DCR, and PFS in paediatric participants
- to evaluate the safety of the combination of CCI [redacted] in paediatric participants
- to characterise the pharmacokinetics (PK) of the combination of niraparib and dostarlimab in paediatric participants
- to assess the immunogenicity of dostarlimab in paediatric participants
- CCI [redacted]

Methodology:

The overall study design and conduct are described in the master protocol.

CCI [redacted]

Under Protocol Amendment 03, enrolment was paused CCI [redacted] This modification is included in Protocol Amendment 05.

CCI [redacted]. Study treatment may continue until progressive disease (PD), unacceptable toxicity, participant withdrawal, Investigator's decision, or death. See Figure 1 for Part 2 study design.

Under Protocol Amendment 05, enrolment in Part 2 will start with a Safety Run-in Cohort to confirm the safety, tolerability, and preliminary efficacy of the CCI [redacted] in participants with osteosarcoma and neuroblastoma. A total of 8 DLT-evaluable participants will be enrolled in the Safety Run-in, with no more than 5 out of 8 evaluable participants having the same tumour type. Participants in the Safety Run-in will be observed for a minimum of 42 days (2 cycles, DLT evaluation period) for DLTs and Grade≥3 thrombocytopenia. Participants in the Safety Run-in will be dosed in a staggered fashion, meaning no more than 3 participants will be allowed to receive study treatment until each dosed participant has completed at least 2 cycles of study treatment and the resulting data from all 3 dosed participants have been reviewed. This is to ensure an adequate interval for observation and assessment of tolerability of the CCI [redacted]

- If DLTs or Grade ≥3 thrombocytopenia are observed in ≤1 participant out of the first 3 dosed participants and it is deemed safe to proceed by the study team, additional participants will be enrolled for up to 8 DLT-evaluable participants.

- If DLTs or Grade ≥3 thrombocytopenia are observed in ≥2 participants out of the first 3 dosed participants, the Part 2 Safety Run-in Cohort will be paused. Review of safety data and available PK data and determination of the dosing strategy for subsequent participants will be completed by the Dose Escalation Committee (DEC; see Appendix 1 of the master protocol for details regarding the DEC).
- The Part 2 Expansion Cohort will be initiated if 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia events are observed out of 8 DLT-evaluable participants.
- The Safety Run-in will be paused if 2 or less DLTs and 3 Grade ≥3 thrombocytopenia events are observed out of 8 DLT-evaluable participants.
- If DLTs are observed in 3 of 8 participants or Grade ≥3 thrombocytopenia is observed in 4 of 8 participants, CCI [redacted] in the Safety Run-in Cohort would be considered intolerable.

Once all participants in the Safety Run-in have been observed for ≥42 days, all available data from the Part 2 Safety Run-in together with all data previously collected under Protocol Amendment 04 or earlier, will be reviewed by the study DEC and the Data Review Committee (DRC) before additional participants on Part 2 are enrolled.

Further details are provided in protocol Section 4.1, including details of the DLTs.

Following the Safety Run-in, if the CCI [redacted] is deemed safe, up to 30 evaluable participants may enrol in the Part 2 Cohort Expansion for osteosarcoma, inclusive of any eligible participants with osteosarcoma treated in the Part 2 Safety Run-in. Enrolment into the Part 2 Cohort Expansion will be conducted according to a Simon's 2-stage optimal design in which ≥2 of the first 10 evaluable participants must achieve PFS6 before accrual of the remaining 20 participants.

CCI [redacted]

General study conduct is described in the master protocol. CCI [redacted]

Data Review Committee

A DRC will be established for the purpose of monitoring safety and efficacy data from the Safety Run-in and cohort expansion part of the study (Part 2). This committee will be composed of GSK staff who are independent of all aspects of the study. Members will include a clinical development physician, a safety physician, and a statistician. This committee will convene both periodically and on an ad hoc basis, as mandated by emerging study data. Comprehensive details of committee membership and its activities will be described in a formal charter.

Number of Participants (Planned): Safety Run-in: approximately 8 DLT-evaluable participants in total across osteosarcoma (Part 2A) and neuroblastoma (Part 2B).

Part 2 Expansion: approximately 30 participants with osteosarcoma are planned for enrolment in this cohort (including eligible participants with osteosarcoma from the Safety Run-in). See Section 9.1 for eligibility requirements for enrolment of Safety Run-in participants into Part 2 Cohort Expansion.

Diagnosis and Main Criteria for Inclusion:

Participant will be eligible for the Safety Run-in and the Osteosarcoma Expansion Cohorts of Part 2 if all of the following criteria are met:

1. CCI [redacted]
2. Participant with osteosarcoma has radiologically measurable disease at screening that can be tracked as RECIST v1.1 target lesion(s).

CCI [redacted]

5. Performance status must be ≥60% on the Karnofsky scale for participants >16 years of age and ≥60% on the Lansky scale for participants ≤16 years of age.

   Note: Neurologic deficits in participants with brain metastases must have been stable for at least 7 days prior to study enrolment. Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status.
6. Participant has adequate organ function, defined as follows:

   Note: The participant must not have received blood transfusion, growth factors, or platelet stimulating agents in the 14 days prior to providing a sample for haematologic analysis nor erythropoietin in the prior 6 weeks.

   a. absolute neutrophil count ≥1000/µL
   b. platelets ≥100 000/µL
   c. haemoglobin ≥8 g/dL or ≥5.0 mmol/L
   d. serum creatinine≤1.5×upper limit of normal (ULN) for age or calculated creatinine clearance or radioisotope glomerular filtration rate ≥60 mL/min/1.73m^2
   e. total bilirubin ≤1.5× ULN or direct bilirubin ≤1 × ULN
   f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case AST and ALT must be ≤5 × ULN
   g. international normalised ratio or prothrombin time (PT) ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
   h. activated PTT ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    a. Is not a woman of childbearing potential (WOCBP).

    or

    b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 of the master protocol, from the Screening Visit through at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
    c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours prior to the first dose of study treatment and irrespective of prior medical treatment.

    Additional requirements for pregnancy testing during and after the Treatment Period are in the master protocol.

    The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
8. A male participant of reproductive potential is eligible to participate if he agrees to the following starting with the first dose of study treatment through at least 90 days (a spermatogenesis cycle) after the last dose of study treatment:
    a. refrain from donating sperm

    plus, either:

    b. be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

    or

    c. must agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant.
9. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.
10. CCI [redacted]

Main Criteria for Exclusion:

Participant will not be eligible for study entry if any of the following criteria are met:

1. Participation presents unacceptable risk to the prospective participant based on the Investigator's judgement.
2. Participant has known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.
3. Participant has received prior therapy with an anti-PD-1, anti-programmed cell death-ligand 1, anti-programmed cell death-ligand 2, anticytotoxic T-lymphocyte-associated antigen-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received dostarlimab).
4. Participant has had prior treatment with a known PARP inhibitor (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received niraparib).
5. Participant has a known history of myelodysplastic syndrome or acute myeloid leukaemia.
6. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying antirheumatic drugs, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
7. Participant has known active central nervous system metastases, carcinomatous meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are clinically stable and have no evidence of new, enlarging, or progressing brain metastases (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks (28 days) prior to the first dose of study treatment. In addition, the participant must not have been using steroids for at least 7 days prior to the first dose of study treatment. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.
8. Participant had a known additional (second primary) malignancy that progressed or required active treatment within the last 2 years.
9. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining assent/consent).
10. Participant has a condition (such as transfusion-dependent anaemia or thrombocytopenia), requirement for therapy, or laboratory abnormality that might confound the study results or interfere with the participant's participation for the full duration of the study treatment.
11. Participant is pregnant, breastfeeding, or expecting to conceive within the projected duration of the study, starting with the Screening Visit through 180 days after the last dose of study treatment.

No data are available regarding the presence of dostarlimab or niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from dostarlimab and/or niraparib, female participants should not breastfeed during treatment with dostarlimab and/or niraparib and for at least 4 months after the last dose of dostarlimab or at least 30 days after the last dose of niraparib, whichever is longer.

12. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
13. Participant has a known history of HIV (type 1 or 2 antibodies).
14. Participant has documented presence of HbsAg and/or HBcAb at Screening or within 3 months prior to first dose of study intervention. Participants with a negative HbsAg and positive HbcAb result are eligible only if HBV DNA is negative (Appendix 12 of the master protocol)
15. Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.
16. Participant has had any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer treatment and that persisted >4 weeks (28 days).
17. Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.
18. Participant had toxicity related to prior immunotherapy that led to treatment discontinuation.
19. Participant had treatment with systemic anticancer therapy (investigational agent or device, or approved chemotherapy, targeted therapy, immunotherapy, or other systemic therapy) within the 3 weeks or 5 half-lives, whichever is shorter, prior to the first dose of study treatment; radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment, or any radiation therapy within 1 week prior to the first dose of study treatment.
20. Participant has not recovered adequately from AEs or complications from any major surgery prior to starting study treatment.
21. Participant has received a live vaccine within 30 days of planned start of study treatment.
22. Participant has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, and history of cerebrovascular accident) within 6 months of enrolment.
23. Participant has heart rate-corrected QT interval prolongation at Screening >450 msec or >480 msec for participants with bundle branch block.

    Notes:

    - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine read or manually over read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual participant must be determined prior to initiation of the study and used consistently for eligibility and study assessments.

24. Participant has received a solid organ transplant.
25. Participant has a documented presence of HCV antibody at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is negative and the participant otherwise meets entry criteria.
26. Participant has a documented presence of HCV RNA at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well.

Investigational Product, Dosage, and Mode of Administration:

CCI [redacted]. Oral niraparib will be dispensed to participants on Day 1 of every 21-day treatment cycle beginning with Cycle 1 of the Treatment Period.

CCI [redacted]

A summary of study treatment administration is provided in the master protocol, and details are in the Pharmacy Manual.

Duration of Treatment: Study treatment may continue until documented PD, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Part 2 Safety Run-in

- DLTs during the first 42 days following the initiation of study treatment (i.e., approximately the first 2 treatment cycles).
- Thrombocytopenia Grade ≥3 AEs during the first 42 days following initiation of study treatment (i.e., approximately the first 2 treatment cycles).
- ORR is defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using International Neuroblastoma Response Criteria (INRC) for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma.
- DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 or INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment or death (whichever occurs first).
- DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment.
- PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment, or death from any cause (whichever occurs first).

Part 2 Efficacy

- PFS6, defined as the proportion of participants without PD per RECIST v1.1 criteria or death at 6 months from the date of the first dose of study treatment.
- ORR, defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using RECIST v1.1.
- DOR, defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 based on Investigator assessment or death (whichever occurs first).
- DCR, defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by RECIST v1.1 based on Investigator assessment.
- PFS, defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by RECIST v1.1 based on Investigator assessment, or death from any cause (whichever occurs first).

The criteria for evaluation of safety, PK, palatability of niraparib, and antidrug antibodies of dostarlimab are described in the master protocol.

Statistical Methods:

Sample Size Consideration

Part 2 Safety Run-In

The statistical gating to initiate the Part 2 Cohort Expansion will be based on minimum of 8 DLT-evaluable participants for DLTs across osteosarcoma and neuroblastoma. When 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia AEs are observed, the study will continue to Part 2 Cohort Expansion. When 3 or more DLTs are observed, the study may not continue to Part 2 Cohort Expansion. When 2 or less DLTs and 3 out of 8 Grade ≥3 thrombocytopenia AEs are observed, the study may be paused for data review. If there is a differential in the DLT-evaluable number of participants to 8 for either endpoint, other criteria may apply and will be specified in the SAP. This will be the primary guideline for the dose recommendations; the totality of data will be taken into account. The probability of initiating Part 2 Cohort Expansion and the probability of pausing for data review are presented in Section 9.1 for 8 DLT-evaluable participants, assuming a weak correlation of 0.15 between the 2 endpoints.

Part 2 Cohort Expansion

The sample size for this cohort is based on a Simon's 2-stage optimal design, with a 1-sided alpha of 0.05 and a minimum power of 80%. The null hypothesis is ≤10% PFS6, and the alternative hypothesis is ≥30% PFS6. A futility analysis will be performed after the initial assessment of response for 10 participants in the cohort. If, among the 10 mITT participants in the cohort, at least 2 participants remain progression-free after 6 months, an additional 19 mITT participants will be enrolled. If 6 or more participants out of the 29 participants remain progression-free after 6 months, the null hypothesis will be rejected. The required sample size of 29 is based on the modified Intent-to-Treat (mITT) Population. The total sample size to be enrolled is planned at approximately 30 in case of the potential lack of sufficient participants in the mITT Population. For consideration of futility, those Part 1 participants who satisfy the inclusion and exclusion criteria of Part 2, satisfy the mITT Population definition, and are treated at the dose used in Part 2 will be included in the Part 2 efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. Under Protocol Amendment 05, osteosarcoma Safety Run-in participants who satisfy the mITT Population definition and are treated at the dose used in the Part 2 Cohort Expansion will also be included in the Part 2 Cohort Expansion efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. The software for the sample size calculation is PASS 2019 (NCSS).

Analysis Populations

- The DLT-evaluable Population consists of participants in Part 2 Safety Run-in who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT for DLT endpoint (or Grade ≥3 thrombocytopenia AEs for the thrombocytopenia endpoint).
- The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
- The Intent-to-Treat Population includes all participants who receive any study medication and have measurable baseline tumour assessment.
- The mITT Population includes all participants who receive any study medication, have measurable baseline tumour assessment, and have at least 1 postbaseline tumour assessment.
- The Per-Protocol Population includes all participants in the mITT Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.
- The PK Population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK Populations are defined separately for each agent.
- Immunogenicity (ADA) Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

General Methods

An overall description of the statistics for this study is provided in the master protocol. Additional details are provided in the Statistical Analysis Plan.

Efficacy Analysis

All analyses will include summary statistics, including number of participants and percentage for categorical variables and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs based on the Clopper-Pearson method will be provided where appropriate (Clopper, 1934). Time-to-event analyses will be performed using Kaplan-Meier methods.

The primary analysis set for the efficacy endpoints will be the mITT Population.

PFS6 and its 2-sided 95% CI will be estimated using the Clopper-Pearson method.

The number and proportion of participants with an objective response will be tabulated. ORR and DCR will be calculated, along with their estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR will be performed using Kaplan-Meier methods, including quartile estimates and 2-sided 95% CI. PFS and its 2-sided 95% CI will be estimated using the Kaplan-Meier method.

CCI [redacted]

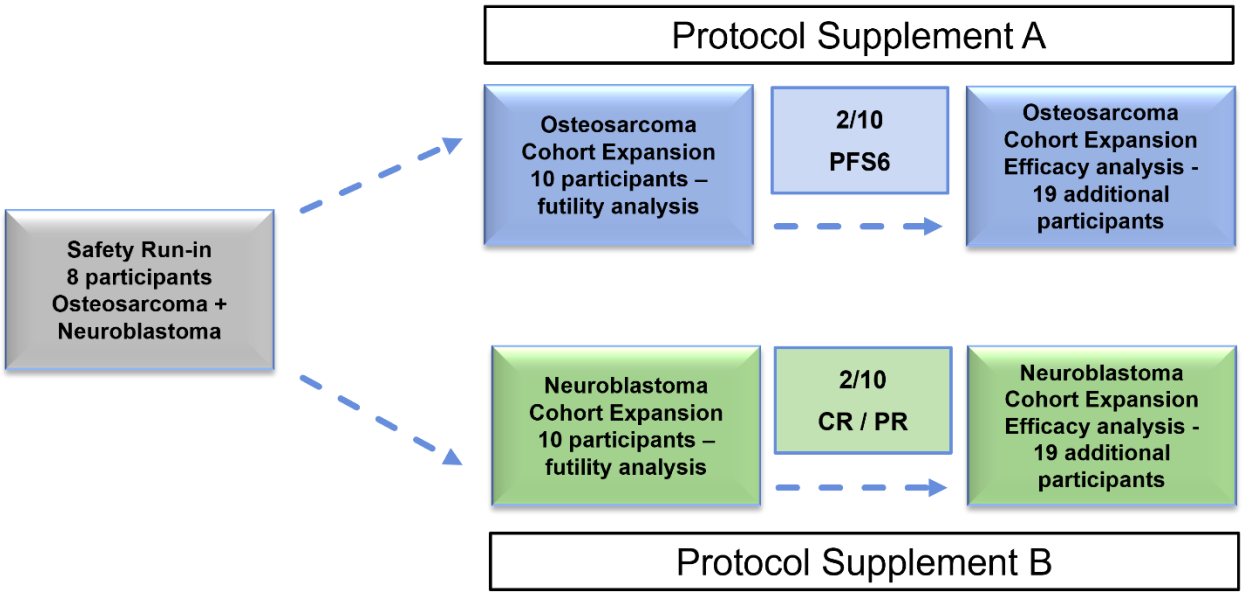
Safety, PK, Immunogenicity, CCI [redacted]

These analyses are described in the master protocol.

1.2. Schemas

Refer to the master protocol for the overall study schema.

Figure 1: Part 2 Study Design



Abbreviations CR=complete response; PFS6=progression-free survival at 6 months; PR=partial response.

1.3. Schedule of Activities (SoA)

The schedule of activities (SoA) for this cohort is provided in Table 3. The tumour assessment flowchart is presented in Table 4.The study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. Regulatory, ethical, and study oversight considerations are provided in Appendix 1 of the master protocol.

Table 3: Schedule of Activities

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment) [b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Informed consent/assent[d]	X								
Demographics and medical history	X								
Performance status	X								
Inclusion/exclusion criteria	X								
CCI									
Physical examination	X	A complete physical examination is to be conducted at Screening and EOT only, and as clinically indicated.							
Psychological assessments[f]	X						X		
Vital signs, weight, and height [g]	X	X	X	X	X	X (Cycle 3 only)	X	X	X

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment) [b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
CBC with differential [h]	X	X (Twice weekly for Safety Run-in only)	X (Twice weekly for Safety Run-in only)	X (Twice weekly for Safety Run-in only)	X		X		
Coagulation [h]	X	As clinically indicated					X		
Blood chemistry [h]	X	X	X	X	X		X		
Serum or urine pregnancy test (WOCBP only) [i]	X	X			X		X	X	X
CCI									
12-lead ECG [k]	X				X (Cycle 3 only)		X		
Dostarlimab administration		X			X				
Niraparib dispensed/collected (administered Day 1 after dostarlimab infusion)		X			X		X (Collect-ion only)		

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment) [b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Tumour assessment: CT or MRI [l,m]	X[n,o]	Every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first[p]					X[q]		
Tumour assessment: Bone scan, whole body MRI, or PET scan [m, r]	X[o]	Required throughout this interval if clinically indicated and to confirm disease response if baseline scan was positive for metastatic bone disease							
CCI [redacted]									
AE monitoring [u]	X	X	X	X	X	X	X	X	X
Prior and concomitant medications and nondrug treatments	X	Medications and nondrug treatments will be monitored for study purposes from Screening to at least 30 days following the last dose of study treatment							
Blood sample for dostarlimab PK and/or ADAs and neutralising antibodies [v, w]		X	X (Cycle 1 only)		X (predose, Cycles 4 and 6, and every 6 cycles thereafter)		X	X	X

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment) [b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Blood sample for niraparib PK [w,x]		X (Cycles 1 and 2 only)	X (Cycle 1 only)						
CCI [redacted]									
Alternative anticancer treatment assessment							X	X	X

Abbreviations: ADA=antidrug antibody; AE=adverse event; AESI=adverse event of special interest; ALP=alkaline phosphatase; BP=blood pressure; CCI [redacted] CBC=complete blood count; CNS=central nervous system; CR=complete response; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; EOT=End of Treatment; FUP=follow-up; G-CSF=granulocyte-colony stimulating factor; HbcAb=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; HCVAb=Hepatitis C virus antibody; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetics; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SAE=serious adverse event; WOCBP=woman of childbearing potential.

a. All participants will undergo an EOT Visit no more than 7 days following the decision to discontinue study treatment for any reason.
b. The Safety FUP Visit and EOT Visit can be combined if both fall within the same window. The Safety FUP Visit is to take place no sooner than 30 days after last dose to permit the protocol-required collection of AEs/SAEs occurring during this 30-day interval. The Safety FUP Visit has a window of +7 days.
c. During the FUP Assessment Period, participants will be followed via clinic visit or telephone contact every 90 (±14) days after the last dose of study treatment for the first year, every 180 (±14) days for the subsequent 2 years, and yearly (±14 days) for an additional 2 years (5 years total), or until the start of alternative antitumour therapy (unless there is an ongoing AE/SAE that must be followed until resolved, stabilised, or otherwise explained), the participant withdraws from the study overall, is lost to follow-up, or dies (whichever occurs earlier).
d. Informed consent/assent must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day Screening Period.
e. CCI [redacted]
f. Psychological assessments to be performed as per local standard of care.

g. Vital signs include temperature, blood pressure, heart rate, and respiratory rate. Vital signs will be taken before, every 15 to 30 minutes during, and at the end of every dostarlimab infusion. Throughout the Treatment Period, all vital signs will be monitored at Week 1 of each cycle even if dostarlimab is not administered. In addition, for the first 8 weeks of the Treatment Period (up to and including Cycle 3 Week 2), all vital signs will be monitored at Week 2 and Week 3 of each cycle. Height and weight will be measured at Screening, Day 1 of each cycle, EOT, 30-day Safety Follow-up, and during the FUP Assessment Period.

h. Haematology, coagulation, and chemistry assessments will be performed by local laboratories. Parameters required in this study are listed in the master protocol. Haematology and chemistry assessments must be measured within 7 days prior to Cycle 1 Day 1 to confirm eligibility. Haematology must be performed and results evaluated prior to study treatment administration. Haematology is to be checked twice each week during the first 2 cycles of study treatment for participants enrolled in Part 2 Safety Run-in and once weekly for participants enrolled in Part 2 Osteosarcoma Expansion Cohort. Haematology tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the participant's study file, and the results must be entered into the eCRF. If dose interruption or modification is required at any point on study because of haematologic toxicity, weekly blood draws for CBC will be done according to Table 8. Additional haematology or chemistry assessments may be performed according to local standard of care or as clinically indicated. If Cycle 1 Day 1 is no more than 7 days following sample collection for Screening, these samples do not need to be collected again for Cycle 1 Day 1, unless clinically warranted. Additional monitoring for haematology is to be performed after a niraparib dose increase due to a birthday or due to a weight increase that moves participants to a higher CCI [redacted], respectively. Haematology is to be checked twice each week during the first 2 cycles after the niraparib dose increase for participants enrolled in the Part 2 Safety Run-in and once weekly for participants enrolled in the Part 2 Osteosarcoma Expansion Cohort. Blood samples should be collected in order of priority as outlined in Section 8.2

i. If the participant is a WOCBP, urine or serum pregnancy test will be performed by the local laboratory at the Screening Visit, within 24 hours prior to the first dose of study treatment, on Day 1 of every cycle for the duration of the Treatment Period, at the EOT Visit, at the 30-Day Safety Follow-up Visit, and 180 (±14) days after the last dose of study treatment. Pregnancy testing should occur irrespective of prior medical treatment. The results from these tests must be available and negative before study treatment is administered. Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected.

j. CCI [redacted]

k. ECG should be repeated at Cycle 3 Week 1 and EOT, as well as during the Treatment or FUP Periods if clinically indicated.

l. CT scans should be performed with contrast agents unless contraindicated for medical reasons. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such a case, CT will be performed without contrast to evaluate the lung parenchyma. If MRI is used to follow-up bone lesion(s), it must be performed prior to any treatment that may affect bone marrow cellularity (eg, G-CSF). PET/CT may be used according to RECIST v1.1 guidelines with full-dose diagnostic CT and as clinically indicated.

m. The same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant. Clinical assessment of superficial lesions should be carried out on the same date as the imaging studies or no later than 3 days thereafter and must be recorded in the participant's eCRF.

n. Participants must have a baseline tumour assessment (CT or MRI) of the chest, abdomen, pelvis, and any additional sites as clinically indicated within 28 days prior to the first dose of study treatment. A baseline brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT scan) is required for participants with previously treated brain metastases. Participants with previously treated brain metastases may participate under the conditions detailed in Exclusion Criterion 7.

o. Radiologic assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations, if all of the following conditions are met:

   (1) the CT or MRI tumour assessments were obtained within 28 days prior to the first dose of study treatment/the bone scan, whole body MRI, or PET tumour assessments were obtained within 84 days prior to the first dose of study treatment,

   (2) the assessments were performed using the method requirements outlined in RECIST v1.1,

   (3) the same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant, and

(4) appropriate documentation indicating that these radiologic tumour assessments were performed as standard of care is available in the participant's source notes.

p. Tumour assessments by CT or MRI of sites involved by disease at baseline and of any additional sites as clinically indicated will be done postbaseline (see Table 4). Tumour assessments should be conducted as outlined in Table 3. Tumour assessments should be scheduled using the date of the first dose of study treatment as the reference date for all time points and are not to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to study treatment delay is not permitted.

q. Participants who have already demonstrated documented PD as per RECIST v1.1 do not need to have tumour assessments repeated at the EOT Visit or during the Post-Treatment FUP. Participants who do not have documented PD at time of study treatment discontinuation; will continue to undergo tumour assessments on their original schedule (i.e., every 9 weeks [every 63 ±7 days] from the start of study treatment for the first 12 months and then every 12 weeks [every 84 ±7 days] thereafter until documented PD, start of alternative anticancer treatment, or discontinuation from overall study participation [eg, death, participant's request, or participant is lost to follow-up], whichever comes first). Participants who have a PR or CR while on treatment and discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.

r. Bone scan, whole body MRI, or PET scans will be carried out at baseline for all participants with osteosarcoma within 84 days prior to the first dose of study treatment in order to detect bony sites of disease. Subsequent assessments are to be performed during the Treatment Period when clinically indicated (i.e., participant describes new or worsening bone pain, or other signs or symptoms of new/progressing bone metastases are present). If the baseline bone scan, whole body MRI, or PET scan is positive for metastatic bone disease, a repeat assessment is required for confirmation of PR or CR.

s. (Footnote intentionally left blank.)

t. Only at Cycle 1 Week1 and Cycle 1 Week 2 for participants who receive CCI niraparib tablets and those who receive CCI

u. AEs will be collected until 30 days after the last dose of study treatment. SAEs will be collected until 90 days after the last dose of study treatment (or to a minimum of 30 days after the last dose of study treatment if the participant starts alternative anticancer treatment). However, any SAEs assessed as related to study participation or related to study treatment will be recorded through the FUP Assessment Period. AESIs must be recorded on the eCRF. AESI collection periods are described in the master protocol. Any pregnancies that occur in female participants within 180 days after the last dose of study treatment or in partners of male participants within 90 days after the last dose of study treatment are to be reported as described in the master protocol. Pregnancies occurring more than 180 days after last dose of study treatment with an associated SAE (considered causally related to the study treatment by the Investigator) will follow the SAE reporting requirements. All AEs and SAEs will be followed, regardless of start of alternative anticancer therapy, until the event is resolved, stabilised, or otherwise explained; or until the participant has withdrawn consent to the study overall, is lost to follow-up (as defined in the master protocol), or has died.

v. Blood samples (single sample for all analytes) for serum dostarlimab PK and/or ADA and neutralising antibodies (NAb) will be collected from participants during Cycle 1 at the following time points relative to the start of the dostarlimab infusion: Cycle 1 Day 1 at Predose (PK, ADA, and NAb) and 1±0.5 hours postdose (PK only), Cycle 1 Day 8 at 168±12 hours postdose (PK, ADA, and NAb), and predose on Cycle 2 Day 1 (predose sample must be collected within 12 hours prior to infusion) (PK, ADA, and NAb). Blood sample for serum dostarlimab PK, ADA, and NAb will also be collected at the following time periods: Predose in Cycles 4 and 6, every 6 cycles thereafter up to 2 years, and the EOT Visit. In addition, blood samples for serum dostarlimab ADA and NAb will be collected at the Safety Follow-up Visit (30 days post-treatment) and at the first Follow-up Visit (90 days post-treatment). PK, ADA, and NAb samples will be drawn at the same time points and in the same collection, except as noted.

w. The maximum blood volume for each sample for PK, ADA, and NAb, and exploratory biomarker assessments is 0.8 mL/kg, and the maximum total blood volume allowed for PK, ADA, and NAb and exploratory biomarker assessments is 1.8 mL/kg per 3-week treatment cycle. Blood samples should be collected in order of priority as outlined in Section 8.2.

x. Blood samples for plasma niraparib and M1 metabolite concentration analyses (single sample for both analytes) will be collected from participants during Cycle 1 Day 1 at 2.5 and 7 hours after the first dose of niraparib, predose on Cycle 1 Day 8, predose on Cycle 2 Day 1, and Cycle 2 Day 1 at 5 hours after niraparib dose. Additional niraparib PK sampling is to be performed after a niraparib dose increase due to a birthday or after a dose modification due to a weight increase or decrease. (These additional PK samples will be taken on Day 1 in the first cycle after the dose change at 2.5 and 7 hours postdose, predose on Day 1 of the second cycle after the dose change, and at 5 hours after

the niraparib dose on Day 1 of the second cycle after the dose change). Note: Predose samples must be collected within 2 hours prior to dosing; Cycle 1 Day 1 2.5 hour samples must be collected at the scheduled time ±0.5 hour and other samples must be collected at the scheduled time ±2 hours.

y. CCI [redacted] Blood samples should be collected in order of priority as outlined in Section 8.2.

Table 4: Tumour Assessment Flowchart

Tumour Assessment	Screening Period	Treatment Period	Confirmation of Response[a]	Post-Treatment Follow-up
CT or MRI of chest, abdomen, pelvis, and any additional sites as clinically indicated	Required	Required, including sites of any other tumour lesions identified at baseline and of any additional sites as clinically indicated	Required, including sites of any other tumour lesions identified at baseline	If PD has been documented: Not required If PD has not been documented: Required, including sites of any other tumour lesions identified at baseline
Brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT)	Required for participants with previously treated brain metastases	Not required unless clinically indicated	Required if baseline scan was positive	Not required unless clinically indicated
Bone scan, whole body MRI, or PET scan	Required	Not required unless clinically indicated	Required if baseline scan was positive for metastatic bone disease	Not required unless clinically indicated
Clinical assessment of superficial lesions	Required	Required for sites of tumour lesions identified at baseline and any additional sites as clinically indicated	Required for sites of tumour lesions identified at baseline	Required for sites of tumour lesions identified at baseline, unless PD has been documented elsewhere

Abbreviations: CT=computed tomography; EOT=End of Treatment; MRI=magnetic resonance imaging; PD=progressive disease.
Note: See Table 3 for detailed guidance on tumour assessment procedures.
a. Participants who have a PR or CR while on treatment and discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation

2. INTRODUCTION

An introduction to the overall study is provided in the master protocol. The objective of the Part 2 Safety Run-in Cohort is to evaluate the safety, tolerability and preliminary efficacy of the [redacted]
The objective of the Expansion Cohort of participants with osteosarcoma (the "OS Cohort") is to assess the antitumour activity of the combination of niraparib and dostarlimab, assessed primarily by the progression-free survival rate at 6 months (PFS6) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria in paediatric participants.

2.1. Background

2.1.1. Background of Niraparib

Overall clinical experience with niraparib is summarised in the master protocol.

2.1.2. Background of Dostarlimab

Overall clinical experience with dostarlimab is summarised in the master protocol.

2.1.3. Rationale for Synergy Between PARP Inhibitors and Immune Checkpoint Inhibitors

The rationale for synergy between poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors and immune checkpoint inhibitors is summarised in the master protocol.

2.2. Rationale for Tumour Type

[redacted]

2.3. Rationale for Current Study

The rationale for the current study is provided in the master protocol.

2.4. Rationale for the Primary Endpoint

While objective response rate (ORR) is typically chosen as a primary endpoint in single-arm studies, RECIST v1.1 is not a tool that can reliably and consistently be utilised for evaluation of drug activity in osteosarcoma as this tumour type tends to stabilise or even increase in radiologically assessed size because of mineralisation of the stromal tissue with tumour necrosis. Objective responses are rare in osteosarcoma, even with proven complete necrosis in the tumour after neoadjuvant chemotherapy in patients with newly diagnosed disease (Lagmay, 2016). Given the limitations of ORR as an endpoint in studies involving participants with osteosarcoma, GSK/TESARO, in consultation with subject matter experts, considered PFS6 as an appropriate endpoint to estimate drug activity in this study. Furthermore, the median interval from initial diagnosis to first recurrence is 1.6 years; the median interval from first to second recurrence is 8

to 9 months; and the median interval between subsequent recurrences remains constant at approximately 6 months (Bielack, 2009), supporting the choice of PFS6 as the primary efficacy endpoint in this cohort.

2.5. Benefit Risk Assessment

The overall benefit risk assessment and dose justification are described in the master protocol.

3. STUDY OBJECTIVES AND PURPOSE

The cohort-specific objectives for this study are defined in Table 5 as follows:

Table 5: Objectives and Endpoints for Study 213406 Osteosarcoma Cohort

Objectives	Endpoints
Part 2 Safety Run-in	
Primary	
Assessment of safety and tolerability of the CCI [redacted] by assessing DLTs and Grade ≥3 thrombocytopenia AEs in paediatric participants	• Assess the incidence of DLTs in the Part 2 Safety Run-in for the DLT-evaluable Population. • Assess the incidence of Grade ≥3 thrombocytopenia AEs in the Part 2 Safety Run-in for the DLT-evaluable Population.
Secondary	
Evaluation of measures of anticancer activity, including ORR, DOR, DCR, and PFS in paediatric participants	ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment or death (whichever occurs first). DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment. PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment, or death from any cause (whichever occurs first).
To evaluate safety of the combination of CCI [redacted] in paediatric participants	Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.

Objectives	Endpoints
To characterise the PK of niraparib in paediatric participants	Niraparib concentrations. PK parameters of niraparib, if appropriate.
Part 2 Expansion	
Primary	
Assessment of the antitumour activity of the combination of CCI [redacted], assessed primarily by PFS6 (using RECIST v1.1 criteria) in paediatric participants	PFS6 is defined as the proportion of participants without PD per RECIST v1.1 criteria or death at 6 months from the date of the first dose of study treatment.
Secondary	
Evaluation of additional measures of anticancer activity including ORR, DOR, DCR, and PFS in paediatric participants	ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using RECIST v1.1. DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 based on Investigator assessment or death (whichever occurs first). DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by RECIST v1.1 based on Investigator assessment. PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by RECIST v1.1 based on Investigator assessment, or death from any cause (whichever occurs first).
Evaluation of the safety of the combination of CCI [redacted] in paediatric participants	Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
Characterisation of the PK of the combination of niraparib and dostarlimab in paediatric participants	Niraparib and dostarlimab concentrations; PK parameters of niraparib and dostarlimab, if appropriate.
Assessment of the immunogenicity of dostarlimab in paediatric participants	Rate and extent of ADAs to dostarlimab.
CCI [redacted]	

Objectives	Endpoints
Exploratory	
CCI [redacted]	

Abbreviations: ADA=antidrug antibody(ies); AE=adverse event; BOR=best overall response; CR=complete response; CCI [redacted] DCR=disease control rate, DLT=dose limiting toxicity; DOR=duration of response; INRC=International Neuroblastoma Response Criteria; imAE=immune-mediated adverse event; ORR=objective response rate; CCI [redacted]; PD=progressive disease; PD-1=programmed cell death protein 1; PFS=progression-free survival; PFS6=progression-free survival rate at 6 months; PK=pharmacokinetic(s); PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SAE(s)=serious adverse event(s); SoA=schedule of activities; TEAE(s)=treatment-emergent adverse event(s); CCI [redacted].

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

CCI

[redacted]

The Part 2 study design is illustrated in Figure 1.

CCI

[redacted]

CCI [redacted]

Once all participants in the Safety Run-in have been observed for ≥42 days, all available data from the Part 2 Safety Run-in together with all data previously collected under Protocol Amendment 04 and earlier, will be reviewed by the study DEC and Data Review Committee (DRC) before additional participants on Part 2 are enrolled.

Following the Safety Run-in, if the CCI [redacted] is deemed safe, up to 30 evaluable participants may enrol in the Part 2 Cohort Expansion for osteosarcoma, inclusive of any eligible participants with osteosarcoma treated in the Part 2 Safety Run-in. Enrolment into the Part 2 Cohort Expansion will be conducted according to a Simon's 2-stage optimal design in which ≥2 of the first 10 evaluable participants must achieve PFS6 before accrual of the remaining 20 participants.

CCI [redacted]

CCI [redacted]

General study conduct is described in the master protocol. CCI [redacted]

4.1.1. Dose Limiting Toxicity

The DLTs and thrombocytopenia toxicities observation period for the Safety Run-in is 42 days following the initiation of study treatment (i.e., approximately the first 2 treatment cycles) in Part 2.

A participant will be considered unevaluable for DLT assessment if, for reasons other than DLT, the participant does not complete the DLT observation period or receives <80% of the intended

niraparib dose (e.g., missed 9 or more doses; reason for missed doses may include, but is not limited to, noncompliance) or <2 infusions of dostarlimab.

A participant will be considered unevaluable for thrombocytopenia events if, for reasons other than thrombocytopenia, the participant does not complete the DLT observation period or receives <80% of the intended niraparib dose (e.g., missed 9 or more doses; reason for missed doses may include, but is not limited to, noncompliance) or <2 infusions of dostarlimab.

Participants considered unevaluable may be replaced after consultation between the Sponsor and Investigator.

A participant may continue on study treatment following a DLT or a thrombocytopenia event if the Investigator determines doing so is in the best interest of the participant, after discussion by the Investigator with the GSK Medical Monitor, and after appropriate recovery from the DLT by the participant.

DLT is defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related Grade 4 nonhaematologic clinical (nonlaboratory) AE
- any treatment-related Grade 3 nonhaematologic clinical (nonlaboratory) AE not resolving to Grade ≤1 within 48 hours of initiating optimal medical intervention
- any treatment-related Grade 3 or 4 nonhaematologic laboratory abnormality if any of the following also occur:
  - the abnormality leads to hospitalisation.
  - the abnormality persists for ≥7 days from the time of AE onset and participant is symptomatic from the AE and/or requires intervention.
- any treatment-related haematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for >7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding or requiring platelet transfusion.
  - Grade 4 neutropenia persists for >7 days, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥72 hours.
  - Grade 4 anaemia or Grade 3 anaemia requiring blood transfusion.
- any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2
- any treatment-related Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks
- any treatment-related Grade ≥2 immune-related endocrine toxicity that requires hormone replacement, except Grade 2 thyroiditis or thyroid dysfunction
- any treatment-related Grade 2 colitis or diarrhoea that persists for ≥7 days without resolution to Grade ≤1 despite adequate steroid therapy
- any Grade 3 or 4 imAE that does not resolve to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy

- Grade 3 or higher infusion-related reaction
- any grade of hemophagocytic lymphohistiocytosis
- any grade of Posterior Reversible Encephalopathy Syndrome (PRES)
- any treatment-related Grade 5 AE

Thrombocytopenia events are defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related toxicity defined as any of the following:
  - Grade 3 or Grade 4 thrombocytopenia

4.2. Number of Participants

Safety Run-in: approximately 8 DLT-evaluable participants in total across osteosarcoma (Part 2A) and neuroblastoma (Part 2B).

Part 2 Expansion: approximately 30 participants with osteosarcoma are planned for enrolment in this cohort (including eligible participants with osteosarcoma from the Safety Run-in). See Section 9.1 for eligibility requirements for enrolment of Safety Run-in participants in the Part 2 Cohort Expansion.

4.3. Treatment Assignment

All participants enrolled in this cohort will receive niraparib in combination with dostarlimab as described in Section 4.1.

4.4. Dose Adjustment Criteria

4.4.1. Dose Adjustment Criteria for Age and Weight

CCI [redacted]

4.4.2. Dose Adjustment for Adverse Events

Adverse reactions should be managed with dose reduction, interruption of treatment, or dose discontinuation.

All dose reductions, treatment delays (including any missed doses) and discontinuations, and the reason for such modifications should be recorded in the eCRF.

It should be noted that required treatment discontinuation of either niraparib or dostarlimab will result in study treatment discontinuation of both treatments.

4.4.3. Niraparib

The recommended dose modifications for adverse reactions should be followed as listed in Table 6, Table 7, and Table 8. Following a dose reduction, participants should not subsequently have dose re-escalated unless a discussion with the GSK Medical Monitor has occurred. Following 2 dose reductions, participants will not be allowed to further dose reduce, and study

treatment should be discontinued. In addition, study treatment should be discontinued for selected AEs that persist beyond 28 days, as noted in Table 7 and Table 8.

CCI

[redacted]

Table 7: Niraparib Dose Modifications for Nonhaematologic Adverse Reactions

NCI CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	• Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6.
NCI CTCAE Grade ≥2 adverse reaction of PRES	• Discontinue study treatment for participants

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; PRES=Posterior Reversible Encephalopathy Syndrome.

There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with PRES. PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

Table 8: Niraparib Dose Modifications for Haematologic Adverse Reactions

Weekly blood draws for CBC will be monitored until the adverse reaction resolves; after resuming niraparib, weekly blood draws for CBC will be required for an additional 4 weeks (28 days) after the adverse reaction has been resolved to the specified levels, after which monitoring at Week 1 of each cycle may resume (**Table 3**).	
Platelet count <100 000/µL	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL. Resume niraparib at the same or lower dose per Table 6. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at the same or reduced dose per Table 6. • If nadir platelet count was <75 000/µL, niraparib dose should be reduced per Table 6.
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6.
Neutrophil <1000/µL or Haemoglobin <8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1000 µL or haemoglobin returns to ≥8 g/dL. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6.
Haematologic adverse reaction requiring transfusion	• For participants with platelet count ≤10 000/µL, platelet transfusion should be considered. If there are other risk factors, such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Red blood cell transfusion(s) may be given at the discretion of the Investigator. • Resume niraparib at a reduced dose per Table 6.
MDS/AML	Any suspected case of MDS/AML reported while a participant is receiving treatment or followed for post-treatment assessments must be referred for evaluation to a local haematologist to perform bone marrow aspirate and biopsy as per local standards of practice. The study site must receive a copy of the haematologist's report of aspirate/biopsy findings, which must include a classification according to the WHO, and other sample testing reports related to MDS/AML. If a diagnosis of MDS/AML is confirmed by a haematologist, the participant must permanently discontinue study treatment.

For clinical situations not covered by this dose modification guidance, the Investigator must contact the GSK Medical Monitor.

4.4.4. Dostarlimab

Dostarlimab dose adjustment criteria are presented in the master protocol.

4.5. Criteria for Study Termination

Criteria for study termination are described in the master protocol.

4.6. End of Study Definition

End of study definition is described in the master protocol.

4.7. Study Conduct

4.7.1. Procedures by Visit

Standard of care tests/procedures, including laboratory assessments, ECG, physical examination, vital signs, height, weight, and performance status, performed before the enrolment into the study can be used as part of the screening assessments as long as the tests/procedures are performed within the visit window indicated in Table 3. Local laboratory assessments (chemistry, haematology) must be performed, and results reviewed no more than 7 days prior to administration of the first dose of study treatment, as indicated in Table 3. Tumour assessment CT or MRI, and bone scan, whole body MRI, or PET scan obtained per the standard of care prior to the first dose of study treatment (within 28 days for CT or MRI and 84 days for bone scan, whole body MRI, or PET scan) do not need to be repeated and are acceptable to use as baseline evaluations if the conditions presented in Section 8.1.2.1 of the master protocol are met. Source documents must clearly identify the standard of care tests/procedures that are used for Screening, and the results of these tests/procedures must be entered in the eCRF. Table 3 details which procedures are performed at each visit.

4.7.2. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic

Due to the significant challenges that currently face the healthcare system and patients due to Coronavirus Disease 2019 (COVID-19), as well as the potential for enduring or additional quarantine measures, the following guidance is being provided in this protocol. In the spirit of global diversity in the COVID-19 pandemic and its impact on healthcare in each individual country as well as the recently issued guidance by several regulatory authorities, the autonomy of each investigative site to assess the benefit/risk for their patients participating in clinical studies should be maintained.

Prior to utilisation of any of the measures outlined in this section, discussion and approval must be obtained from Sponsor/contract research organisation.

It is expected that sites participating in clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the SoA (Table 3). The use of local laboratories and local radiology centres to reduce the need

for a participant to come into the clinic are supported, if deemed necessary for the well-being of the participant. These local facilities should be added to regulatory documents, as required.

Additionally, regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring programs to maintain oversight of clinical sites. Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor/contract research organisation.

General rules for participants with limited possibility to travel are as follows:

- If possible, replace in-person visits with phone contact or alternative location for assessment (eg, local laboratories and imaging centres).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Participant Inclusion Criteria

Participants will be eligible for the Safety Run-in and Osteosarcoma Expansion Cohort of Part 2 if all of the following criteria are met:

1. CCI [redacted]
2. Participant with osteosarcoma has radiologically measurable disease at screening that can be tracked as RECIST v1.1 target lesion(s).

CCI [redacted]

5. Performance status must be ≥60% on the Karnofsky scale for participants >16 years of age and ≥60% on the Lansky scale for participants ≤16 years of age.

   Note: Neurologic deficits in participants with brain metastases must have been stable for at least 7 days prior to study enrolment. Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status.

6. Participant has adequate organ function, defined as follows:

   Note: The participant must not have received blood transfusion, growth factors, or platelet stimulating agents in the 14 days prior to providing a sample for haematologic analysis nor erythropoietin in the prior 6 weeks.

   a. absolute neutrophil count ≥1000/µL
   b. platelets ≥100 000/µL
   c. haemoglobin ≥8 g/dL or ≥5.0 mmol/L

d. serum creatinine≤1.5×upper limit of normal (ULN) for age or calculated creatinine clearance or radioisotope glomerular filtration rate ≥60 mL/min/1.73m^2
e. total bilirubin ≤1.5× ULN or direct bilirubin ≤1 × ULN
f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case AST and ALT must be ≤5 × ULN
g. international normalised ratio or prothrombin time (PT) ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
h. activated PTT ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   a. Is not a woman of childbearing potential (WOCBP).

   or

   b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 of the master protocol, from the Screening Visit through at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
   c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours prior to the first dose of study treatment and irrespective of prior medical treatment.

   Additional requirements for pregnancy testing during and after the Treatment Period are in the master protocol.

   The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. A male participant of reproductive potential is eligible to participate if he agrees to the following starting with the first dose of study treatment through at least 90 days (a spermatogenesis cycle) after the last dose of study treatment:

   a. refrain from donating sperm

   plus, either:

   b. be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

   or

   c. must agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant

9. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.
10. CCI [redacted]

5.2. Participant Exclusion Criteria

Participants will not be eligible for study entry if any of the following criteria are met:

1. Participation presents unacceptable risk to the prospective participant based on the Investigator's judgement.
2. Participant has known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.
3. Participant has received prior therapy with an anti-PD-1, anti-programmed cell death-ligand 1, anti-programmed cell death-ligand 2, anticytotoxic T-lymphocyte-associated antigen-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received dostarlimab).
4. Participant has had prior treatment with a known PARP inhibitor (except for participants rolling over from Part 1 of the study: these participants are allowed to have received niraparib).
5. Participant has a known history of myelodysplastic syndrome or acute myeloid leukaemia.
6. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying antirheumatic drugs, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
7. Participant has known active central nervous system metastases, carcinomatous meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are clinically stable and have no evidence of new, enlarging, or progressing brain metastases (using the identical imaging modality for each assessment,

either MRI or CT scan) for at least 4 weeks (28 days) prior to the first dose of study treatment. In addition, the participant must not have been using steroids for at least 7 days prior to the first dose of study treatment. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.

8. Participant had a known additional (second primary) malignancy that progressed or required active treatment within the last 2 years.
9. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining assent/consent).
10. Participant has a condition (such as transfusion-dependent anaemia or thrombocytopenia), requirement for therapy, or laboratory abnormality that might confound the study results or interfere with the participant's participation for the full duration of the study treatment.
11. Participant is pregnant, breastfeeding, or expecting to conceive within the projected duration of the study, starting with the Screening Visit through 180 days after the last dose of study treatment.

    No data are available regarding the presence of dostarlimab or niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from dostarlimab and/or niraparib, female participants should not breastfeed during treatment with dostarlimab and/or niraparib and for at least 4 months after the last dose of dostarlimab or at least 30 days after the last dose of niraparib, whichever is longer.
12. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
13. Participant has a known history of HIV (type 1 or 2 antibodies).
14. Participant has documented presence of HbsAg and/or HBcAb at Screening or within 3 months prior to first dose of study intervention. Participants with a negative HbsAg and positive HbcAb result are eligible only if HBV DNA is negative (Appendix 12 of the master protocol).
15. Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.
16. Participant has had any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer treatment and that persisted >4 weeks (28 days).

17. Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic therapy-induced adverse events (AEs). Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.
18. Participant had toxicity related to prior immunotherapy that led to treatment discontinuation.
19. Participant had treatment with systemic anticancer therapy (investigational agent or device, or approved chemotherapy, targeted therapy, immunotherapy, or other systemic therapy) within the 3 weeks or 5 half-lives, whichever is shorter prior to the first dose of study treatment, radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment, or any radiation therapy within 1 week prior to the first dose of study treatment.
20. Participant has not recovered adequately from AEs or complications from any major surgery prior to starting study treatment.
21. Participant has received a live vaccine within 30 days of planned start of study treatment.
22. Participant has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, and history of cerebrovascular accident) within 6 months of enrolment.
23. Participant has heart rate-corrected QT interval prolongation at Screening >450 msec or >480 msec for participants with bundle branch block.

    Notes:

    - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine read or manually over read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual participant must be determined prior to initiation of the study and used consistently for eligibility and study assessments.
24. Participant has received solid organ transplant.
25. Participant has a documented presence of HCV antibody at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is negative and the participant otherwise meets entry criteria.
26. Participant has a documented presence of HCV RNA at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well.

5.3. Lifestyle Considerations

Cases of photosensitivity have been reported for patients on niraparib treatment. Participants must be informed on measures to decrease exposure to ultraviolet light, such as minimising time in direct sunlight unless wearing hats and long-sleeves and application of sun protection creams.

5.4. Screen Failures

The definition of a screen failure is provided in the master protocol.

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

CCI [redacted]

Niraparib will be dispensed to participants on Day 1 of every 21-day treatment cycle.

The niraparib dosing regimens under Protocol Amendment 05 are shown in master protocol.

CCI [redacted]

Details about the investigational products are provided in Table 9.

Table 9: Investigational Products

	Investigational Product		
Intervention name	Niraparib	Niraparib	Dostarlimab
Type	Drug	Drug	Biologic
Dosage form	CCI [redacted]		
Unit dose			
Route of administration			
Use	IMP	IMP	IMP
Authorised AxMP/ Unauthorised AxMP	Not applicable	Not applicable	Not applicable
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Physical description (Packaging and Labelling; see Section 6.2.1)	CCI [redacted]		
Dose level(s)	See master protocol	See master protocol	See master protocol
Manufacturer	WuXi STA (WuXi), China (DS, DP) Dishman, India (DS) Corden, Colorado, US (DS) Mayne Pharma, Raleigh, North Carolina, US (DP) Siegfried, Switzerland (DS)	WuXi STA (WuXi), China (DS, DP) Corden, Colorado, US (DS) Dishman, India (DS) Siegfried, Switzerland (DS)	WuXi Biologics (WuXi), Wuxi, China (DS) Ajinomoto Althea (Aji), San Diego, California, US (DP)

Abbreviations: AxMP = auxiliary medicinal product; DP=drug product; DS=drug substance; IMP = investigation medicinal product; IV=intravenous; Non-IMP = non-investigational medicinal product; CCI [redacted]; US=United States.

Further details on the study interventions are provided in the master protocol and respective IBs.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Treatment Packaging and Labelling

Overall study treatment packaging and labelling are described in the master protocol.

6.2.2. Study Treatment Storage

Study treatment storage is described in the master protocol.

6.2.3. Administration

Details on the administration of the study treatments can be found in the Pharmacy Manual. A summary is provided in the master protocol.

6.2.4. Study Treatment Accountability

Study treatment accountability is described in the master protocol.

6.2.5. Study Treatment Handling and Disposal

Study treatment handling and disposal are described in the master protocol.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomised, open-label study.

6.4. Study Treatment Compliance

Overall study treatment compliance information is presented in the master protocol. Study treatment (dostarlimab and niraparib during dostarlimab infusion visits) will be administered by investigational site personnel at investigational sites.

6.5. Dose Modification

Dose reductions for dostarlimab are not permitted while participant is being treated on study. Dosing may be held in the event of an AE which may be deemed related to treatment. If 2 or more consecutive dostarlimab doses are held, Investigator must notify the GSK Medical Monitor for approval to continue treatment of the participant on study.

Refer to Section 4.4 for full dose modification guidance for niraparib and Section 4.7 in the master protocol for full dose modification guidance for dostarlimab.

6.6. Treatment of Overdose

This information is described in the master protocol.

6.7. Concomitant Therapy

Details on the definition and recording of concomitant medications are provided in the master protocol.

6.7.1. Rescue Medications

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including but not limited to the items outlined in Section 6.8.1 of the master protocol.

6.7.2. Prohibited Medications

Known prior medications that exclude a participant from participating in this cohort are described in the exclusion criteria (see Section 5.2).

Medications prohibited in the overall study are provided in the master protocol.

6.7.3. Other Study Restrictions

Other study restrictions are provided in the master protocol.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Guidance on discontinuation of study treatment is described in the master protocol.

7.1.1. Liver Chemistry Stopping Criteria

Specific guidance on liver chemistry stopping criteria is described in the master protocol in Section 7.1.1 and Appendix 8. Guidance on drug restart or rechallenge following liver safety events, if applicable, is included in Appendix 9 of the master protocol.

7.1.2. QTc Stopping Criteria

Guidance on QTc stopping criteria is described in the master protocol.

7.2. Withdrawal of Consent

Procedures to be followed in cases of consent withdrawal are presented in the master protocol.

7.3. Participant Discontinuation/Withdrawal from the Study

Examples of reasons for discontinuing study treatment or study are applicable across cohorts and are presented in the master protocol.

Guidance on discontinuation of participants from the study, including required actions for participants lost to follow-up, is provided in the master protocol.

7.4. Lost to Follow-Up

Guidance on required actions for participants lost to follow-up is provided in the master protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Assessment of Efficacy

The timing of radiologic evaluations and details regarding the evaluation of tumour response for both the Part 2 Safety Run-in and the Part 2 Osteosarcoma Expansion Cohort are provided in Table 3 and in the master protocol. Participant scan data are not routinely collected in this study; however, such data may be requested under special circumstances such as during investigation of a significant safety event.

8.1.1. Primary Efficacy Endpoint for the Osteosarcoma Cohort Expansion

The primary efficacy endpoint for this cohort will be PFS6, defined as the proportion of participant without PD per RECIST v1.1 criteria or death at 6 months from the date of the first dose of study treatment.

8.1.2. Secondary Efficacy Endpoints for the Osteosarcoma Cohort Expansion

The secondary endpoints for this cohort will be ORR, DOR, DCR, and PFS based on Investigator assessment using RECIST v1.1.

8.1.2.1. Objective Response Rate

ORR is defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using RECIST v1.1.

8.1.2.2. Duration of Response

DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmed CR or PR. Participants who do not experience PD or who die after they have had a response are censored at the date of their last tumour assessment.

8.1.2.3. Disease Control Rate

DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by RECIST v1.1 based on Investigator assessment.

8.1.2.4. Progression-free Survival

PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by RECIST v1.1 based on Investigator assessment, or death from any cause (whichever occurs first). Participants without an event will be censored at the date of the last tumour assessment. Participants without postbaseline assessments will be censored at the date of the first dose.

CCI [redacted]

8.2. Assessment of Safety

Planned time points for all safety assessments are provided in Table 3.

At some timepoints, the protocol may specify that blood samples for clinical care (i.e., clinical chemistry, haematology, pregnancy) and for study-related research (PK, exploratory biomarkers) be obtained during a single study visit. In the event of concern for excessive blood volume withdrawal sample collection should be prioritised as follows:

1. clinical care
2. niraparib PK
3. dostarlimab PK, ADA, and NAb
4. CCI [redacted]

8.2.1. Safety Parameters

Safety parameters for this study are described in the master protocol.

8.3. Adverse Events and Serious Adverse Events

Definitions and guidance on AEs and SAEs are provided in the master protocol.

8.4. Pharmacokinetics, Immunogenicity, and Biomarkers

Blood samples to assess niraparib PK, dostarlimab PK, and dostarlimab antidrug antibodies (ADAs) and NAb will be collected from all participants pre- and postdose at the time points specified in Table 3. CCI [redacted]

Sample collection should be prioritised as outlined in Section 8.2.

Additional details concerning PK and immunogenicity sample collection are provided in the master protocol.

CCI [redacted]

CCI

[redacted]

8.6. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

An overall description of the statistics for this study is provided in the master protocol. Additional details are provided in the Statistical Analysis Plan.

9.1. Sample Size Determination

Part 2 Safety Run-In

The statistical gating to initiate the Part 2 Cohort Expansion will be based on minimum of 8 DLT-evaluable participants for DLTs across osteosarcoma and neuroblastoma. When 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia AEs are observed, the study will continue to Part 2 Cohort Expansion. When 3 or more DLTs are observed, the study may not continue to Part 2 Cohort Expansion. When 2 or less DLTs and 3 out of 8 Grade ≥3 thrombocytopenia AEs are observed, the study may be paused for data review. If there is a differential in the DLT-evaluable number of participants to 8 for either endpoint, other criteria may apply and will be specified in the SAP. This will be the primary guideline for the dose recommendations; the totality of data will be taken into account. The probability of initiating Part 2 Cohort Expansion and the probability of pausing for data review are presented in the table below for 8 DLT-evaluable participants, assuming a weak correlation of 0.15 between the 2 endpoints.

True DLT Rate	True Grade ≥3 Thrombocytopenia Rate	Probability of Initiating Part 2 Cohort Expansion (2 or Less DLTs and 2 or Less Grade ≥3 Thrombocytopenia Events Observed Out of 8 DLT-evaluable Participants)	Probability of Pausing for Data Review (3 Grade ≥3 Thrombocytopenia Events and 2 or Less DLTs Observed Out of 8 DLT-evaluable Participants)
0.25	0.25	49%	13%
0.30	0.25	40%	10%
0.30	0.30	32%	13%
0.35	0.35	21%	11%
0.45	0.45	6%	6%

Part 2 Cohort Expansion

The sample size for this cohort is based on a Simon's 2-stage optimal design, with a 1-sided alpha of 0.05 and a minimum power of 80%. The null hypothesis is ≤10% PFS6, and the alternative hypothesis is ≥30% PFS6. A futility analysis will be performed after the initial assessment of response for 10 evaluable participants in the cohort. If, among the 10 mITT participants in the cohort, at least 2 participants remain progression-free after 6 months, an additional 19 mITT participants will be enrolled. If 6 or more participants out of the 29 participants enrolled remain progression-free after 6 months, the null hypothesis will be rejected. The required sample size of 29 is based on the modified Intent-to-Treat (mITT) Population. The total sample size to be enrolled is planned at approximately 30 in case of the potential lack of sufficient participants in the mITT Population. For consideration of futility, those Part 1 participants who satisfy the inclusion and exclusion criteria of Part 2, satisfy the

mITT Population definition, and are treated at the dose used in Part 2 Cohort Expansion will be included in the Part 2 efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. Under Protocol Amendment 05, osteosarcoma Safety Run-in participants who satisfy the mITT Population definition and are treated at the modified dose used in the Part 2 Cohort Expansion will also be included in the Part 2 Cohort Expansion efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. The software for the sample size calculation is PASS 2019 (NCSS).

9.2. Analysis Populations

For the purposes of analysis, the following analysis sets are defined as follows in Table 10.

Table 10: Analysis Sets

Participant Analysis Set	Description
DLT-evaluable	The DLT-evaluable Population consists of participants in Part 2 Safety Run-in who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT for DLT endpoint (or Grade ≥3 thrombocytopenia AEs for the thrombocytopenia event endpoint).
Safety	The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
Intent-to-Treat (ITT)	The ITT Population includes all participants who receive any study medication and have measurable baseline tumour assessment.
Modified Intent-to-Treat (mITT)	The mITT Population includes all participants who receive any study medication, have measurable baseline tumour assessment, and have at least 1 postbaseline tumour assessment.
Per-Protocol	The Per-Protocol Population includes all participants in the mITT Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.
Pharmacokinetic (PK)	The PK Population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK Populations are defined separately for each agent.
Immunogenicity (ADA) Population	The ADA Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

9.3. Statistical Analyses

9.3.1. General Considerations

All analyses will include summary statistics, including number of participants and percentage for categorical variables and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs based on the Clopper-Pearson method will be provided where appropriate (Clopper, 1934). Time-to-event analyses will be performed using Kaplan-Meier methods.

The primary analysis set for the efficacy endpoints will be the mITT Population.

9.3.2. Primary Endpoints

The primary endpoints for the Safety Run-in and Part 2 Osteosarcoma Cohort Expansion are defined in Section 3; the primary endpoint for the Part 2 Osteosarcoma Cohort Expansion is also defined in Section 8.1.1.

For the Safety Run-in, the incidence of DLTs and incidence of Grade ≥3 thrombocytopenia AEs will be summarised in the DLT-evaluable Population.

For the Part 2 Osteosarcoma Cohort Expansion, PFS6 and its 2-sided 95% CI will be estimated using the Clopper-Pearson method.

9.3.3. Secondary Endpoints

The secondary endpoints for the Safety Run-in and Part 2 Osteosarcoma Cohort Expansion are outlined in Section 3 and, for Part 2 Osteosarcoma Cohort Expansion, also in Section 8.1.2.

The number and proportion of participants with an objective response will be tabulated. ORR and DCR will be calculated, along with their estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR will be performed using Kaplan-Meier methods, including quartile estimates and 2-sided 95% CI. PFS and its 2-sided 95% CI will be estimated using the Kaplan-Meier method.

9.3.3.1. Safety Analyses

Safety analyses of this study are described in the master protocol.

9.3.3.2. PK Analysis

PK analyses in this study are described in the master protocol.

CCI [redacted]

9.3.3.4. Immunogenicity Analysis

Immunogenicity analysis in this study is described in the master protocol.

CCI

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The regulatory and ethical considerations of the study are outlined in Appendix 1 of the master protocol.

11. APPENDICES

The following appendices in the master protocol should be referenced for the necessary guidance for this cohort.

Appendix 1	Regulatory, Ethical, and Study Considerations
Appendix 2	Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting
Appendix 3	Contraception Guidelines
Appendix 4	Guidelines for Assessment of Disease, Disease Progression and Response Criteria – Adapted from RECIST 1.1
Appendix 6	List of Abbreviations and Definitions of Terms
CCI [redacted]	
Appendix 8	Liver Safety: Required Actions and Follow-up Assessments
Appendix 9	Liver Safety Drug Restart or Rechallenge Guidelines
Appendix 12	Consideration for Participants with Past HBV Infection

APPENDIX 1. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 01 (16 October 2020)

Overall Rationale for Amendment 01

Amendment 01 revised the protocol requirement for tumour assessments to be aligned with current standard of care and provides other clarifications and editorial changes catalogued since the issuance of the prior version of the protocol. Additionally, minor changes to the time allowed for safety reporting to ensure consistency with GSK standard practices.

Summary of Changes for the Amendment

Table 2 Summary of Changes for Amendment 01

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this version.	Editorial changes to align with the Sponsor's standard protocol template and ways of working and inclusion of specific language noted during Health Authority review
Section 1.3 Schedule of Activities	Revision to footnote for vital signs assessment to include guidance for blood pressure monitoring Deletion of minimum body weight criteria for PK parameters Revision of language for collection of information for SAEs and AEs	Alignment with niraparib safety monitoring in accordance with Investigator's Brochure, and Package Insert/Summary of Product Characteristics Deletion of information inadvertently propagated throughout protocol in error Removal of discrepant information and improved clarity
Section 1.3 Schedule of Activities Table 4 Tumour Assessment Flowchart	Revision of preferred imaging types and schedule for scans; additionally, Schedule of Activities revised to separate imaging assessments according to different timings for standard of care and type of assessments	Allowable imaging types and schedule revised to align with current standard of care

Section(s) Affected	Description of Change	Brief Rationale
Section 4.7.1 Procedures by Visit	Revision of preferred imaging types and schedule for scans	Allowable imaging types and schedule revised to align with current standard of care
Section 4.7.2 General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic	New section added	Additional guidance to sites included in light of COVID-19
Synopsis Section 5.1 Inclusion Criteria	Minimum threshold of performance status reduced to 60% in Inclusion #4 Criteria for adequate CBC collection result revised to 1 week in Inclusion #5 Minimum threshold of absolute neutrophil count reduced to ≥1,000/μL in Inclusion #5	Revision to align with standard of care Revision to align with standard of care Revised safety monitoring guidance
Section 9.2 Analysis Populations	Immunogenicity populations included	Provided for clarity as to analysis populations intended to be studied

Abbreviations: AE=adverse event; CBC=complete blood count; COVID-19=Coronavirus Disease 2019; PK=pharmacokinetic; SAE=serious adverse event.

Amendment 02 (23 November 2020)

Overall Rationale for the Amendment

Amendment 02 revises the protocol to include specific safety language noted during Health Authority review as detailed in Table 2.

Summary of Changes for the Amendment

Table 2: Summary of Changes for Amendment 02

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, Appendix 1. Protocol Amendment History (new), and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment and administrative information for prior amendment was moved to new Appendix 1. Protocol	Editorial changes to align with the Sponsor's standard protocol template and ways of working, for conformity, clarity, flow, and typographical error correction, and for inclusion of specific language noted during Health Authority review

Section(s) Affected	Description of Change	Brief Rationale
	Amendment History. Editorial changes made throughout.	
Section 1.1. Synopsis (Main Criteria for Inclusion) Section 5.1. Participant Inclusion Criteria	Clarified that participants must not be eligible for local curative treatment (criterion 1)	Participants who are eligible for local curative treatment are not permitted in the study
Section 1.1. Synopsis (Main Criteria for Exclusion) Section 5.2. Participant Exclusion Criteria	Added language for exclusion in cases of pregnant or breastfeeding participants (criterion 11) Modified that a participant should not have received a live vaccine within 30 days of starting study treatment (criterion 20) (changed from 14 days) Clarified that participants with QT interval prolongation >480 ms at screening are not eligible and no waivers are allowed (criterion 22)	Participants who are pregnant or breastfeeding are excluded from the study Participants must not receive live vaccines within 30 days of starting study treatment Participants with QT interval prolongation >480 ms at screening are not eligible for the study
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities (footnote c)	Clarified that, during the long-term Follow-Up Assessment Period, follow-up might be conducted via a clinic visit or telephone contact	To accurately reflect study conduct
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities, Table 4: Tumour Assessment Flow Chart	Updated Table 3 and Table 4 to reflect editorial updates made in the master protocol	To align with the master protocol
Section 5.3. Lifestyle Considerations	Added that participants should avoid exposure to ultraviolet light and take precautions when exposed to direct sunlight	Added due to the fact that photosensitivity has been reported for patients receiving niraparib

Amendment 03 (20 Jul 2022)

Overall Rationale for Amendment 03:

- To update secondary objective and/or endpoint for PK and immunogenicity.
- To update inclusion and exclusion criteria.
- To increase clarity and/or remove discrepancies.

All changes are listed in table below.

Table 2: Summary of Changes for Amendment 03

Section(s) Affected	Description of Change	Brief Rationale
Headers, title page, Protocol Amendment Summary of Changes, Appendix 1. Protocol Amendment History, and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment and administrative information for prior amendment was moved to Appendix 1. Protocol Amendment History. Editorial changes made throughout.	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Title page	Updated compound number "GSK4057190 to GSK4057190A"	To present current correct compound number
Section 1.1 Synopsis (Secondary objectives) Section 3 Study Objectives and Endpoints	Added new secondary objective; to assess the immunogenicity of dostarlimab in paediatric participants	To correct lack of secondary objective given immunogenicity analyses are described in the protocol and an immunogenicity population is defined in Section 9 Statistical Considerations
CCI [redacted]		
Section 1.1 Synopsis (Methodology) Data Review Committee	Updated information for establishment and composition of an independent data oversight committee	To clarify that a committee that is independent of all aspects of the study and that is dedicated to oversight of safety and efficacy data from participants in Part 2 will be established. To clarify that details of committee composition and function will be described in a formal charter.
CCI [redacted]		To indicate that the RP2D CCI [redacted] as determined in Part 1A of the study is the dose that is to be advanced and evaluated in Part 2 of the study.

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 6) Section 5.1. Participant Inclusion Criteria (criterion 6)	Updated note describing timing for collection of blood sample for complete blood count	To better describe a correct and more reasonable washout period for support agents (transfusion, colony-stimulating factors, erythropoietin) received prior to collection of blood for complete blood count during screening.
CCI [redacted]		
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 10) Section 5.2. Participant Exclusion Criteria (criterion 10)	Removed bullets on blood transfusion and growth factors in exclusion criterion 10	Permitted window prior to first dose of study treatment has been updated in inclusion criterion 5. The permitted windows in exclusion criterion 10 no longer are applicable and, therefore, were removed.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 15) Section 5.2. Participant Exclusion Criteria (criterion 15)	Deleted original exclusion criterion 15 (this text was combined with text for exclusion criterion 19 as described below) and replaced with “Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc”	To update exclusion criteria to include additional criterion to support participant safety.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 16) Section 5.2. Participant Exclusion Criteria (criterion 16)	Updated exclusion criteria 16 to clarify guidance on hematologic side effects from prior anticancer therapy.	To clarify information on excluded cytopenia occurrence and duration

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 18) Section 5.2: Participant Exclusion Criteria (criterion 18)	Added new exclusion criteria "Toxicity related to prior immunotherapy that led to study treatment discontinuation."	To include guidance for enrolment of patients who had previously experienced toxicity in response to immunotherapy and to align eligibility requirements with those of dostarlimab protocols in general.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 19) Section 5.2. Participant Exclusion Criteria (criterion 15) Section 5.2. Participant Exclusion Criteria (criterion 19)	• Deleted original exclusion criterion 15. • Updated exclusion criterion 19 to clarify permitted window relative to first dose of study treatment for prior systemic anticancer therapy. Combined text from exclusion criterion 15 with text in exclusion criterion 19.	To update permitted window for receipt of prior anticancer therapy from "within 3 weeks" prior to first dose of study treatment to "within 3 weeks or 5 half-lives, whichever is shorter" - a change which was made in response to an investigator's suggestion and which reflects half-life data for most common standard of care therapies enrolled patients with the specified tumour types. In addition, to make the excluded window consistent for investigational agents or devices and for approved systemic therapies of all types.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 23) Section 5.2. Participant Exclusion Criteria (criterion 23)	Updated exclusion criterion 23 with corrected QTc values and added instructional text.	To align excluded QTc values with values appropriate for participants to be treated with dostarlimab.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 24) Section 5.2. Participant Exclusion Criteria (criterion 24)	Added exclusion criteria 24 to clarify that solid organ transplant is not permitted.	To prohibit enrolment of participants who are receiving immunosuppressive therapy that might impact effectiveness of dostarlimab as a PD-1 inhibitor.
Section 1.1. Synopsis (Analysis Population) Section 9.2 Analysis Population Table 7	Revised definition of PK population and immunogenicity populations	To more accurately describe which participants qualified for inclusion in each population
Section 1.3. Schedule of Activities (Table 3)	Added "Post Treatment" to column header for FUP assessment Period	To align column header content with text clarifying that Follow-up visits were to occur every 90 days following end of study treatment.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (Table 3)	Removed -10-day window from Screening period	To correct outside limit of Screening activities window to -28 days rather than -28 days +10 additional days.
Section 1.3. Schedule of Activities (Table 3 and Footnote j)	Addition of pregnancy testing for WOCBP at End of Treatment and 30-day Safety Follow-up Visits	To ensure pregnancy did not occur during the excluded period.
Section 1.3. Schedule of Activities (Table 3 and Footnote l)	Addition of 12-lead ECG testing added in Cycle 3	In line with study level requirements
Section 1.3 Schedule of Activities (Table 3 and Footnote q, r)	Added text indicating that tumour assessments should be conducted every 9 weeks (every 63 [±7] days) from the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter,	To reduce total number of scans conducted throughout duration of participant enrolment and thereby reduce radiation exposure overall.
Section 1.3 Schedule of Activities (Table 3)	Merged cells for EOT Visit, Safety FUP Visit, and FUP Assessment Period for the rows for several disease assessment activities	To clarify that measures of disease assessment are to continue throughout the EOT and follow-up periods.
Section 1.3. Schedule of Activities (Table 3 Footnote b)	Added additional details on safety FUP visit	To clarify the Safety FUP visit window
Section 1.3. Schedule of Activities (Table 3 Footnote c)	Clarified long-term follow-up assessment period 90 (±14) days “after the last dose of study treatment”	To clearly define specific starting point from which to initiate long-term follow-up safety assessments
Section 1.3. Schedule of Activities (Table 3 Footnote i)	Updated to replace baseline with “Cycle 1 Day 1” and to clarify guidance for Cycle 1 Day 1 sample collection.	To clarify that if the screening laboratory samples were collected within 7 days prior to Cycle 1 Day 1, then collection of these samples did not need to be repeated for Cycle 1 Day 1.
Section 1.3 Schedule of Activities (Table 3 Footnote m)	Removed the language that “MRI should only be used if clinically appropriate, when CT is contraindicated, and preferably for imaging of the brain”	To remove restrictions to use of MRI in medically appropriate scanning situations

Section(s) Affected	Description of Change	Brief Rationale
CCI		
Section 1.3 Schedule of Activities (Table 3 Footnote v)	Added text clarifying required duration of AE collection	To clarify that collection of AEs is to continue throughout the required 30-day interval even in the event of initiation of additional anticancer treatment.
Section 1.3 Schedule of Activities (Table 3 Footnote y)	Added text clarifying collection interval for PK sample collection	To clarify that timing of PK sample collection is relative to time of participant's very first dose of niraparib.
Section 1.3. Schedule of Activities (Table 3 Footnote w, x and z)	Updated information for dostarlimab PK, ADA, neutralising antibodies, and biomarker sample collection	To provide additional guidance for procedures and timing of dostarlimab PK, ADA, and biomarker sampling.
Section 2.5 Benefits and Risks Assessment	Added new section and referred to master protocol	To align content of protocol with that of GSK standard template
Section 3 Study Objectives and Endpoints	Revised PK endpoint	To describe the parameters constituting the endpoint measures.
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Added "non-randomized"	To clarify study design
Section 6.4. Study Treatment Compliance	Added "dostarlimab and niraparib during dostarlimab infusion visits".	To clarify exactly what study treatment would be administered to the participant at the research site and when this treatment would be administered.
Section 6.5 Dose Modification	Added clarifying text	To clarify that guidance in first paragraph of Section 6.5 is applicable to dostarlimab. To include reference to Section 4.7 in the master protocol for full dose modification guidance.

Section(s) Affected	Description of Change	Brief Rationale
Section 6.8 Treatment Compliance	Deleted this Section	To remove text that had already been presented in the protocol in Section 6.4.
Section 7.1.2 QTc Stopping Criteria	Added new section on QTc stopping criteria referring to master protocol	To align with safety monitoring requirements for dostarlimab
Section 8.1.2 Secondary Efficacy Endpoint	Added text for scan data collection	To establish that while scan data are not routinely collected in the study, these data may be collected under special circumstances.
Section 8.4 Pharmacokinetics, Immunogenicity and Biomarkers	• Added text from Master protocol Section 8.4 on PK sampling.	To provide additional detail in this supplement protocol on PK sampling requirements.
CCI [redacted]		
Section 9.3.3 Secondary Endpoints, Section 9.3.4 Interim Analysis, and Section 9.3.5 Exploratory Analysis	Reordered sections / subsections	Reordered sections/ subsections to more clearly present planned analyses.

Amendment 04 (23 May 2024)

Overall Rationale for Amendment 04:

Amendment 04 is a global amendment resulting in changes in participant dosing based on the participant's age. Administrative, editorial, and clarifications for study conduct are also included. A general description and brief rationale(s) for key changes are provided in Table 2 below. The synopsis was also updated to align with the changes in the protocol body.

Table 2 Summary of Changes for Amendment 04

Section(s) Affected	Description of Change	Brief Rationale
Headers, Title Page, abbreviations, Protocol Amendment Summary of Changes, List of Abbreviations, Appendices, References, and throughout Section 6 Study Treatments and Concomitant Therapy	Headers and title page updated with new document numbers, dates, and amendment information; Protocol Amendment Summary of Changes section was updated to include details and rationales for this amendment; administrative changes, abbreviation updates, editorial revisions for consistency with Sponsor's ways of working, minor corrections and formatting adjustments, and to add clarification and/or remove discrepancies	Editorial changes to align with the Sponsor's standard protocol template, style guide, ways of working, regulatory requirements, and for accuracy, clarity, conformity, flow, and typographical error correction.
Throughout	• Use of CCI changed to CCI throughout the document including CCI details and use of CCI going forward	CCI is the selected CCI [redacted] developed by the applicant for use in participants and is a term commonly used by the Sponsor's formulation development and manufacturing groups
Section 1.3 Schedule of Assessments (Table 3, footnote) Section 1.2 Schemas, Figure 1 (new) Section 2 Introduction Section 3, Table 5: Objectives and Endpoints for Study 213406 Section 4.1 Overall Design Section 4.1.1 Dose Limiting Toxicity Section 4.2 Number of Participants Section 4.4 Dose Adjustment Criteria Section 4.4.1 Dose Adjustment Criteria for Age and Weight Section 4.4.2 Dose Adjustments for Adverse Events Section 4.4.3 Niraparib Section 4.4.4 Dostarlimab Section 5.1 Participant Inclusion Criterion Section 6.1 Study Treatments Administered Table 9: Investigational Products Section 8.1 Assessment of Efficacy Section 9.1 Sample Size Determination Section 9.2 Analysis Populations Section 9.3.2 Primary Endpoints Section 9.3.3 Secondary Endpoints	• New figure outlining Part 2 study design • Footnotes updated in SoA regarding monitoring/PK sample collection with changes in niraparib doses in new proposed niraparib dosing regimens • Introduction and study objectives and endpoints updated to include the Safety Run-in Cohort • Update overall design to reflect updated dosing and details of Safety Run-in • DLT criteria for Part 2 included in new section • Number of participants updated to include Safety Run-in Cohort participants • Section 4.4.1 and Section 4.4.2 added outlining dose adjustments for age and weight and AEs • Section 4.4.3 included for guidance on niraparib dose reductions and Table 6, Table 7, and Table 8 added outlining modifications for AEs, nonhematologic adverse reactions, and haematologic adverse reactions, respectively • Subsection included for dostarlimab dose modification • Inclusion Criterion #3 updated to outline age enrolment requirements under Amendment 04	Changes to proposed dosing regimens for niraparib and study design, following study enrolment pause and data evaluation to ensure appropriate dosing of participants with the combination, including additional cohorts to evaluate additional dose levels Minor editorial changes to endpoints and objectives for clarification.

Section(s) Affected	Description of Change	Brief Rationale
	• Inclusion criterion #4 – updated to reflect no requirement for ability to swallow as a result of CCI formulation being used going forward • Study treatment information sections update to include CCI details including update to Investigation products table that also included updates to align with regulatory requirements • Sample size text updated to reflect addition of Safety Run-in • Updated assessment of efficacy section and statistical analyses sections to include Safety Run-in information and definition for DTL-evaluable Population	
Section 3, Table 5 Objectives and Endpoints for Study 213406 Section 9.3.5 Exploratory analyses	• Exploratory endpoints updated to adjust wording for exploratory biomarker objective and endpoint language, as well as analyses	To provide further details and more clarity about the planned exploratory analysis.
Section 5.1 Participant Inclusion Criteria	• Inclusion criterion #6: organ function parameters updated for haemoglobin	To align with the patient population
Section 1.3 Schedule of Assessments (Table 3, footnote) Section 5.1 Participant Inclusion Criteria (criterion #7c)	• Clarification included that WOCBP must have a pregnancy test even if they had received treatment that potentially but not definitely would prohibit becoming pregnant • Timeline for providing negative pregnancy test result updated to 24 hours	Updated to increase assurance that female participant of childbearing potential is not pregnant as close as possible to time of study drug dosing
Section 5.2 Participant Exclusion Criteria	• Exclusion criterion #7 – clarification participants with previously treated CNS metastases for evidence of disease progression, for evidence of disease progression	Updated text to provide more accurate description of changes indicative of progression of disease in brain.
Section 5.2 Participant Exclusion Criteria	• Exclusion criterion #11 - updated language regarding when breastfeeding can resume	To align with guidance in current US prescribing information for niraparib and dostarlimab
Section 5.2. Participant Exclusion Criteria	• Exclusion criterion 14 – updated wording regarding HbsAg/HbcAb for HBV screening	To permit the inclusion of patients with past HBV infection
Section 5.2. Participant Exclusion Criteria	• New exclusion criteria #25 and #26 added regarding HCV testing	To align with current protocol template language
Section 5.2. Participant Exclusion Criteria	• Exclusion criterion #17 – updated language regarding AEs in participants undergoing systemic anticancer therapy with exceptions as agreed with Sponsor.	Expansion of text to more clearly define conditions for participant eligibility.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments (Table 3, including footnotes)	CCI [redacted]	
Section 2.2 Rationale for Tumour Type	• CCI [redacted]	Editorial change for clarification
Section 5.1. Participant Inclusion Criteria	• Inclusion criterion #1 - Replaced statement 'local curative treatment.' with 'alternative curative treatment.'	Clarification
Section 5.1 Participant Inclusion Criteria	• Inclusion criterion #10 – updated clarifying tumour tissue sample requirements and decalcification for bone samples	Clarification
Section 1.3. Schedule of Activities (Table 3, including footnote) Section 4.4 General Study Conduct Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	• Update to blood sample collection for niraparib PK • Adjusted table and added clarifying footnote for blood sampling for dostarlimab PK and/or ADAs and neutralising antibodies (NAb) at Safety FUP Visit and FUP Assessment Period • Updated language regarding collection of blood samples and storage	Clarification for study conduct and alignment with Sponsor requirements for sample storage
Section 1.3 Schedule of Assessments (Table 3 and Table 4; including footnotes) Table 4 Tumour Assessment Flowchart	• Clarification that brain scans must include IV contrast and brain scan by MRI preferred to that by CT including in table footnote and Table 4 outlining tumour assessments • Wording and footnote updates in SoA for clarifications including aligning discontinuation wording throughout	Clarification for study conduct.
Section 1.3 Schedule of Assessments (SoA) footnote Section 8.2 Assessment of Safety Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	• Detail included regarding prioritisation of blood sample collection in the event of concerns for excessive blood volume withdrawal	Clarification for study conduct to provide guidance to sites on relative importance of collection of specific blood samples
Section 1.3 Schedule of Assessments (SoA) including footnote Section 8.4.1 Exploratory biomarkers	• Updated language regarding collection and analysis of biomarker samples and processing	Clarification
Section 1.3. Schedule of Activities (Table 3, including footnotes)	• Updated timing for collection of vital signs, height, and weight measurements including during follow-up period and clarifications for measuring height and weight • CCI [redacted]	Clarification for study conduct, including adjusted language to permit consistent monitoring of vital signs throughout the Treatment Period.

Section(s) Affected	Description of Change	Brief Rationale
	• Adjusted wording surrounding collection and follow-up of nonserious AEs, and expectations for follow-up of SAEs during long-term Follow-up Period and when starting alternative anticancer therapy	
Section 8.5 Genetics	• Updated language outlining DNA analysis	Clarification

Abbreviations: CCI [redacted] ADA=antidrug antibody(ies); AE=adverse event; CCI [redacted]; CBC=complete blood count; CNS=central nervous system; CT=computed tomography; DLT=dose limiting toxicity(ies); FUP=follow-up; GFR=glomerular filtration rate; HbcAb=hepatitis B core antibody, HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; PK=pharmacokinetics; RECIST=Response Evaluation Criteria in Solid Tumours; SAE(s)= serious AE(s); SoA=schedule of assessments; CCI [redacted]; WOCBP=woman of childbearing potential; US=United States.

Amendment 04 GBR-1(08 Aug 2024)

Overall Rationale for Amendment 04 GBR-1:

Amendment 04 GBR-1 is a UK-specific amendment addressing agency feedback regarding exclusion criterion 17. A description and rationale for the changes is provided in Table 2 below

Table 2: Summary of Changes for Amendment 04 GBR-1

Section(s) Affected	Description of Change (~~deleted text~~; **added text**)	Brief Rationale
Headers, Title Page, Protocol Amendment Summary of Changes, Appendix 2 Country-specific Requirements	Headers and title page updated with new amendment number/approval date, and amendment information; Protocol Amendment Summary of Changes section was updated to include details and rationale for this amendment; country-specific appendix for global amendments removed and associated text in protocol sections/tables adjusted.	Editorial changes to align with the Sponsor's standard protocol template, style guide, ways of working.
Synopsis Section 5.2 Participant Exclusion Criteria	Exclusion criterion #17 updated as follows: Participant has not recovered (i.e., to Grade ≤1 or to baseline) from systemic **anticancer** therapy-induced AEs. Note: Participants with ~~certain AEs that are considered either nonclinically significant or are deemed stable or irreversible are exceptions to this criterion and may qualify for the study after discussion with the GSK Medical Monitor. Examples of AEs include, but are not limited to, alopecia,~~ hearing impairment, **alopecia**, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/**or** Grade ≤2 neutropenia **are an exception to this criterion and may qualify for the study.**	Regulatory agency feedback.

CCI

[redacted]

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 17-Dec-2024 15:54:13 GMT+0000

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TITLE PAGE

SUPPLEMENT B

PROTOCOL 213406

PART 2: NEUROBLASTOMA EXPANSION COHORT

Protocol Title:	A PHASE 1, MULTICENTRE, OPEN-LABEL, DOSE ESCALATION AND COHORT EXPANSION STUDY OF NIRAPARIB AND DOSTARLIMAB IN PAEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMOURS
Protocol Number:	213406 Amendment 05
Compound Number or Name:	Niraparib (GSK3985771), Dostarlimab (GSK4057190A)
Brief Title:	Dose Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Participants With Solid Tumours
Study Phase:	Phase 1
Sponsor Name and Legal Registered Address:	GlaxoSmithKline Research & Development Limited 79 New Oxford Street London WC1A 1DG United Kingdom
Medical Monitor Name and Contact Information:	Contact Information can be found in local study contact information
Sponsor Signatory:	Nidale Tarek, MD Senior Medical Director GSK
Regulatory Agency Identifying Number(s):	EudraCT Number: 2020-002359-39 EU CT: 2024-511071-16
Approval Date:	17 Dec 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date
Amendment 05	17 Dec 2024
Amendment 04 GBR-1	08 August 2024
Amendment 04	23 May 2024
Amendment 03	20 July 2022
Amendment 02	23 November 2020
Amendment 01	16 October 2020
Original Protocol	12 May 2020

Amendment 05 (17 Dec 2024)

Overall rationale for the current Amendment:

Protocol Amendment 05 is a substantial amendment that aligns Protocol Amendment 04 with all aspects of the UK-specific Protocol Amendment 04 GBR-1, resulting in a single global amendment. Additional changes include an update of the sponsor's legal registered address plus administrative and editorial updates and clarifications for study conduct.

A general description and brief rationale(s) for key changes are provided in Table 2 below. The synopsis was also updated to align with the changes in the protocol body, where applicable.

Table 2 List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Title Page	Sponsor legal address update	To align with current GSK policy
Section 1.1 Synopsis Methodology] Section 4.1 Overall Study Design	Language updated to indicate that the dose escalation committee (DEC) will review safety data and will determine future enrollment plan	To more clearly describe the role of the DEC in safety data review process overall
Section 1.1 Synopsis Main Criteria for Inclusion; Section 5.1 Participant Inclusion Criteria Point 03	Addition of relevant time point ("at screening")	To clearly indicate at what point in the study disease characteristics were to be evaluated
Section 1.1 Synopsis Main Criteria for Exclusion; Section 5.2 Participant Exclusion Criteria Point 17	Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic anticancer therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this	To revert the wording to that in Protocol Amendment 04, which provided more specific criteria for enrollment of participants with ongoing toxicities.

Section # and title	Description of change	Brief rationale
	criterion and may qualify for participation in the study.	
CCI [redacted]		
Section 1.3 Schedule of Activities (SoA) Footnote x	"Cycle 1 Day 1 2.5 hour samples must be collected at the scheduled time ±0.5 hour" was added	To more specifically define the permitted sample collection window
Section 1.3 Table 3 Schedule of Activities Table 4 Tumor Assessment Flowchart	Addition of text indicating bone marrow evaluation is required for all participants to confirm response.	To clarify timing of required bone marrow assessments during response evaluation
Section 1.1 Synopsis Objectives Section 3 STUDY OBJECTIVES AND PURPOSE Table 5	Text was added to Part 2 Safety Run-in Secondary Objective for general standard safety objective	To ensure that all safety data were assessed in Part 2 Safety Run-in not just DLTs and events of Grade ≥3 thrombocytopenia
CCI [redacted]		
Throughout document	Minor corrections and formatting adjustments were made	To add clarification and increase readability

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: GSK
Name of Investigational Product: Niraparib, dostarlimab
Name of Active Ingredient: Niraparib, dostarlimab
Title of Study: A Phase 1, Multicentre, Open-label, Dose escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients with Recurrent or Refractory Solid Tumours **Part 2: Neuroblastoma Expansion Cohort**
Study Centre(s): Multicentre
CCI [redacted] **Phase of Development:** Phase 1

Objectives:

The following are the objectives for the Safety Run-in Cohort and Neuroblastoma Expansion Cohort of this study.

Part 2 Safety Run-In

Primary:

The primary objective of this cohort is as follows:

- to assess the safety and tolerability of the CCI [redacted] by assessing dose limiting toxicity (DLT) and Grade ≥3 thrombocytopenia adverse events (AEs) in paediatric participants

Secondary:

The secondary objectives of this cohort are as follows:

- to evaluate additional measures of anticancer activity, including objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) in paediatric participants
- to characterise the pharmacokinetics (PK) of niraparib in paediatric participants
- to evaluate the safety of the combination CCI [redacted] in paediatric participants

Part 2 Expansion

Primary:

The primary objective of this cohort is as follows:

- to assess the antitumour activity of the combination of niraparib and dostarlimab, assessed primarily by ORR (using International Neuroblastoma Response Criteria [INRC]) in paediatric participants

Secondary:

The secondary objectives of this cohort are as follows:

- to evaluate additional measures of anticancer activity, including DOR, DCR, and PFS in paediatric participants
- to evaluate the safety of the combination of CCI [redacted] in paediatric participants
- to characterise the pharmacokinetics (PK) of the combination of niraparib and dostarlimab in paediatric participants
- to assess the immunogenicity of dostarlimab in paediatric participants
- CCI [redacted]

Methodology:

The overall study design and conduct are described in the master protocol.

CCI [redacted]

CCI [redacted] This modification is included in Protocol Amendment 05.

CCI [redacted]. Study treatment may continue until progressive disease (PD), unacceptable toxicity, participant withdrawal, Investigator's decision, or death. See Figure 1 for Part 2 study design.

Under Protocol Amendment 05, enrolment in Part 2 will start with a Safety Run-in Cohort to confirm the safety, tolerability, and preliminary efficacy of the CCI [redacted] in participants with osteosarcoma and neuroblastoma. A total of 8 DLT-evaluable participants will be enrolled in the Safety Run-in, with no more than 5 out of 8 evaluable participants having the same tumour type. Participants in the Safety Run-in will be observed for a minimum of 42 days (2 cycles, DLT evaluation period) for DLTs and Grade≥3 thrombocytopenia. Participants in the Safety Run-in will be dosed in a staggered fashion, meaning no more than 3 participants will be allowed to receive the study treatment until each dosed participant has completed at least 2 cycles of study treatment and the resulting data from all 3 dosed participants have been reviewed. This is to ensure an adequate interval for observation and assessment of tolerability of the CCI [redacted]

- If DLTs or Grade ≥3 thrombocytopenia are observed in ≤1 participant out of the first 3 dosed participants and it is deemed safe to proceed by the study team, additional participants will be enrolled for up to 8 DLT-evaluable participants.
- If DLTs or Grade ≥3 thrombocytopenia are observed in ≥2 participants out of the first 3 dosed participants, the Part 2 Safety Run-in Cohort will be paused. Review of safety data and available PK data and determination of the dosing strategy for subsequent participants will be completed by the Dose Escalation Committee (DEC; see Appendix 1 of the master protocol for details regarding the DEC).
- The Part 2 Expansion Cohort will be initiated if 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia events are observed out of 8 DLT-evaluable participants.
- The Safety Run-in will be paused if 2 or less DLTs and 3 Grade ≥3 thrombocytopenia events are observed out of 8 DLT-evaluable participants.
- If DLTs are observed in 3 of 8 participants or Grade ≥3 thrombocytopenia is observed in 4 of 8 participants, CCI [redacted] in the Safety Run-in Cohort would be considered intolerable.

Once all participants in the Safety Run-in have been observed for ≥42 days, all available data from the Part 2 Safety Run-in together with all data previously collected under Protocol Amendment 04 and earlier will be reviewed by the study DEC and the Data Review Committee (DRC) before additional participants on Part 2 are enrolled.

Further details are provided in protocol Section 4.1, including details of the DLTs.

Following the Safety Run-in, if the CCI [redacted] is deemed safe, up to 30 evaluable participants may enrol in the Part 2 Cohort Expansion for neuroblastoma, inclusive of any eligible participants with neuroblastoma treated in the Part 2 Safety Run-in. Enrolment into the Part 2 Cohort Expansion will be conducted according to a Simon's 2-stage optimal design in which ≥2 of the first 10 evaluable participants must experience an objective tumour response (as assessed by the Investigator using INRC) before accrual of the remaining 20 participants.

CCI [redacted]

General study conduct is described in the master protocol. CCI [redacted]

Data Review Committee

A DRC will be established for the purpose of monitoring safety and efficacy data from the Safety Run-in and Cohort Expansion part of the study (Part 2). This committee will be composed of GSK staff who are independent of all aspects of the study. Members will include a clinical development physician, a safety physician, and a statistician. This committee will convene both periodically and on an ad hoc basis, as mandated by emerging study data. Comprehensive details of committee membership and its activities will be described in a formal charter.

Number of Participants (Planned): Safety Run-in: approximately 8 DLT-evaluable participants in total across osteosarcoma (Part 2A) and neuroblastoma (Part 2B).

Part 2 Expansion: approximately 30 participants with neuroblastoma are planned for enrolment in this cohort (including eligible participants with neuroblastoma from the Safety Run-in). See Section 9.1 for eligibility requirements for enrolment of Safety Run-in participants into the Part 2 Cohort Expansion.

Diagnosis and Main Criteria for Inclusion:

Participant will be eligible for the Safety Run-in and Neuroblastoma Expansion Cohorts of Part 2 if all of the following criteria are met:

1. CCI [redacted]
2. Participant with neuroblastoma has measurable/evaluable disease by INRC at screening. Participants with recurrent/relapsed bone metastasis that is metaiodobenzylguanidine (MIBG)-positive (or FDG-positive, for MIBG-nonavid tumours) as only site of disease are eligible.

CCI [redacted]

5. Performance status must be ≥60% on the Karnofsky scale for participants >16 years of age and ≥60% on the Lansky scale for participants ≤16 years of age.

   Note: Neurologic deficits in participants with brain metastases must have been stable for at least 7 days prior to study enrolment. Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status.
6. Participant has adequate organ function, defined as follows:

   Note: The participant must not have received blood transfusion, growth factors, or platelet stimulating agents in the 14 days prior to providing a sample for haematologic analysis nor erythropoietin in the prior 6 weeks.

   a. absolute neutrophil count ≥1000/µL
   b. platelets ≥100 000/µL
   c. haemoglobin ≥8 g/dL or ≥5.0 mmol/L
   d. serum creatinine≤1.5×upper limit of normal (ULN) for age or calculated creatinine clearance or radioisotope glomerular filtration rate ≥60 mL/min/1.73m^2
   e. total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 × ULN

f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case AST and ALT must be ≤5 × ULN

g. international normalised ratio or prothrombin time (PT) ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants

h. activated PTT ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   a. Is not a woman of childbearing potential (WOCBP).

   Or

   b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 of the master protocol, from the Screening Visit through at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.

   c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours prior to the first dose of study treatment and irrespective of prior medical treatment.

   Additional requirements for pregnancy testing during and after the Treatment Period are located in the master protocol.

   The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. A male participant of reproductive potential is eligible to participate if he agrees to the following starting with the first dose of study treatment through at least 90 days (a spermatogenesis cycle) after the last dose of study treatment:

   a. refrain from donating sperm

   plus, either:

   b. be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

   or

   c. must agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant

9. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.

10. CCI [redacted]

CCI [redacted]

Main Criteria for Exclusion:

Participant will not be eligible for study entry if any of the following criteria are met:

1. Participation presents unacceptable risk to the prospective participant based on the Investigator's judgement.
2. Participant has known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.
3. Participant has received prior therapy with an anti-PD-1, anti-programmed cell death-ligand 1, anti-programmed cell death-ligand 2, anticytotoxic T-lymphocyte-associated antigen-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received dostarlimab).
4. Participant has had prior treatment with a known PARP inhibitor (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received niraparib).
5. Participant has a known history of myelodysplastic syndrome or acute myeloid leukaemia.
6. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying antirheumatic drugs, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
7. Participant has known active central nervous system (CNS) metastases, carcinomatous meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are clinically stable and have no evidence of new, enlarging, or progressing brain metastases (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks (28 days) prior to the first dose of study treatment. In addition, the participant must not have been using steroids for at least 7 days prior to the first dose of study treatment. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.
8. Participant had a known additional (second primary) malignancy that progressed or required active treatment within the last 2 years.
9. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining assent/consent).
10. Participant has a condition (such as transfusion-dependent anaemia or thrombocytopenia), requirement for therapy, or laboratory abnormality that might confound the study results or interfere with the participant's participation for the full duration of the study treatment.

11. Participant is pregnant, breastfeeding, or expecting to conceive within the projected duration of the study, starting with the Screening Visit through 180 days after the last dose of study treatment.

    No data are available regarding the presence of dostarlimab or niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from dostarlimab and/or niraparib, female participants should not breastfeed during treatment with dostarlimab and/or niraparib and for at least 4 months after the last dose of dostarlimab or at least 30 days after the last dose of niraparib, whichever is longer.

12. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
13. Participant has a known history of HIV (type 1 or 2 antibodies).
14. Participant has documented presence of HbsAg and/or HBcAb at Screening or within 3 months prior to first dose of study intervention. Participants with a negative HbsAg and positive HbcAb result are eligible only if HBV DNA is negative (Appendix 12 of the master protocol)
15. Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.
16. Participant has had any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer treatment and that persisted >4 weeks (28 days).
17. Participant has not recovered (ie, to Grade ≤1 or to baseline) from prior systemic therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.
18. Participant had toxicity related to prior immunotherapy that led to treatment discontinuation.
19. Participant had treatment with prior systemic anticancer therapy (investigational agent or device, or approved chemotherapy, targeted therapy, immunotherapy, or other systemic therapy) within the 3 weeks or 5 half-lives, whichever is shorter, prior to the first dose of study treatment, radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment, or any radiation therapy within 1 week prior to the first dose of study treatment.
20. Participant has not recovered adequately from AEs or complications from any major surgery prior to starting study treatment.
21. Participant has received a live vaccine within 30 days of planned start of study treatment.
22. Participant has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, and history of cerebrovascular accident) within 6 months of enrolment.
23. Participant has heart rate-corrected QT interval prolongation at Screening >450 msec or >480 msec for participants with bundle branch block.

    Notes:

- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine read or manually over read.
- The specific formula that will be used to determine eligibility and discontinuation for an individual participant must be determined prior to initiation of the study and used consistently for eligibility and study assessments.

24. Participant has received a solid organ transplant.
25. Participant has a documented presence of HCV antibody at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is negative and the participant otherwise meets entry criteria.
26. Participant has documented presence of HCV RNA at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well.

Investigational Product, Dosage, and Mode of Administration:

CCI [redacted] Oral niraparib will be dispensed to participants on Day 1 of every 21-day treatment cycle beginning with Cycle 1 of the Treatment Period.

CCI [redacted]

A summary of study treatment administration is provided in the master protocol, and details are in the Pharmacy Manual.

Duration of Treatment: Study treatment may continue until documented PD, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Part 2 Safety Run-in

- DLTs during the first 42 days following the initiation of study treatment (i.e., approximately the first 2 treatment cycles).
- Thrombocytopenia Grade ≥3 AEs during the first 42 days following initiation of study treatment (i.e., approximately the first 2 treatment cycles).
- ORR is defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma.
- DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC for participants with neuroblastoma only or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment or death (whichever occurs first).
- DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment.

- PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment, or death from any cause (whichever occurs first).

Part 2 Efficacy

- ORR, defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using INRC.
- DOR, defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC based on Investigator assessment or death (whichever occurs first).
- DCR, defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC based on Investigator assessment.
- PFS, defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC based on Investigator assessment, or death from any cause (whichever occurs first).

The criteria for evaluation of safety, PK, palatability of niraparib, and antidrug antibodies of dostarlimab are described in the master protocol.

Statistical Methods:

Sample Size Consideration

Part 2 Safety Run-in

The statistical gating to initiate the Part 2 Cohort Expansion will be based on minimum of 8 DLT-evaluable participants for DLTs across osteosarcoma and neuroblastoma. When 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia AEs are observed, the study will continue to Part 2 Cohort Expansion. When 3 or more DLTs are observed, the study may not continue to Part 2 Cohort Expansion. When 2 or less DLTs and 3 out of 8 Grade ≥3 thrombocytopenia AEs are observed, the study may be paused for data review. If there is a differential in the DLT-evaluable number of participants to 8 for either endpoint, other criteria may apply and will be specified in the SAP. This will be the primary guideline for the dose recommendations, the totality of data will be taken into account. The probability of initiating Part 2 Cohort Expansion and the probability of pausing for data review are presented in Section 9.1 for 8 DLT-evaluable participants, assuming a weak correlation of 0.15 between the 2 endpoints.

Part 2 Cohort Expansion

The sample size for this cohort is based on a Simon's 2-stage optimal design, with a 1-sided alpha of 0.05 and a minimum power of 80%. The null hypothesis is ≤10% ORR, and the alternative hypothesis is ≥30% ORR. A futility analysis will be performed after the initial assessment of response for 10 evaluable participants in the cohort. If, among the 10 mITT participants in the cohort, at least 2 participants have objective responses (CR or PR), an additional 19 mITT participants will be enrolled. If 6 or more participants out of the 29 participants enrolled have objective responses, the null hypothesis will be rejected. The required sample size of 29 is based on the modified Intent-to-Treat (mITT) Population. The total sample size to be enrolled is planned at approximately 30 in case of the potential lack of sufficient participants in the mITT Population. For consideration of futility, those Part 1 participants who satisfy the inclusion and exclusion criteria of Part 2, satisfy the mITT Population definition, and are treated at the dose used in Part 2 will be included in the Part 2 Cohort Expansion efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. Under Protocol Amendment 05, neuroblastoma Safety Run-in participants who satisfy the mITT Population definition and are treated at the dose used in the Part 2 Cohort Expansion will also be included in the

Part 2 Cohort Expansion efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. The software for the sample size calculation is PASS 2019 (NCSS).

Analysis Populations

- The DLT-evaluable Population consists of participants in Part 2 Safety Run-in who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT for DLT endpoint (or Grade ≥3 thrombocytopenia AEs for the thrombocytopenia event endpoint).
- The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
- The Intent-to-Treat Population includes all participants who receive any study medication and have measurable baseline tumour assessment and/or MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid tumours) at baseline.
- The mITT Population includes all participants who receive any study medication, have measurable baseline tumour assessment and/or MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid tumours) at baseline, and have at least 1 postbaseline tumour assessment.
- The Per-Protocol Population includes all participants in the mITT population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.
- The PK Population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK populations are defined separately for each agent.
- Immunogenicity (ADA) Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

General Methods

An overall description of the statistics for this study is provided in the master protocol. Additional details are provided in the Statistical Analysis Plan.

Efficacy Analysis

All analyses will include summary statistics, including number of participants and percentage for categorical variables and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% Cis based on the Clopper-Pearson method will be provided where appropriate (Clopper, 1934). Time-to-event analyses will be performed using Kaplan-Meier methods.

The primary analysis set for the efficacy endpoints will be the mITT Population.

The number and proportion of participants with an objective response will be tabulated. ORR and DCR will be calculated, along with their estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR will be performed using Kaplan-Meier methods, including quartile estimates and 2-sided 95% CI. PFS and its 2-sided 95% CI will be estimated using the Kaplan-Meier method.

CCI [redacted]

CCI [redacted]

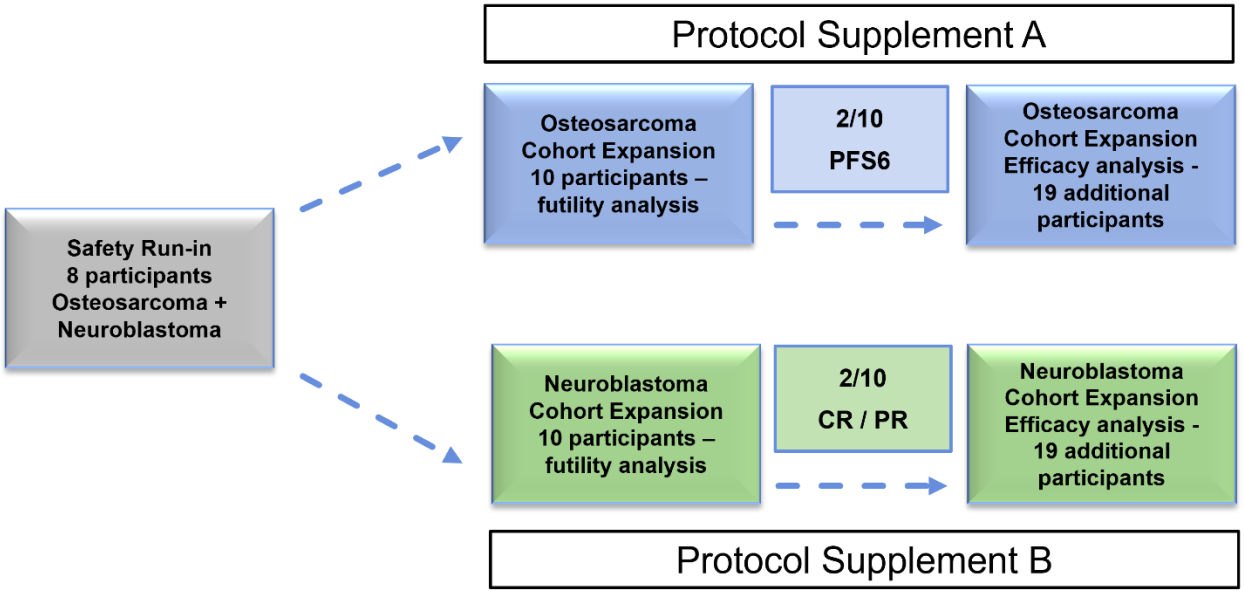
Safety, PK, Immunogenicity, and CCI [redacted]

These analyses are described in the master protocol.

1.2. Schemas

Refer to the master protocol for the overall study schema.

Figure 1: Part 2 Study Schema



Abbreviations: CR=complete response; PFS6=PFS at 6 months; PR=partial response.

1.3. Schedule of Activities (SoA)

The schedule of activities (SoA) for this cohort is provided in Table 3. The tumour assessment flowchart is presented in Table 4.The study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. Regulatory, ethical, and study oversight considerations are provided in Appendix 1 of the master protocol.

Table 3: Schedule of Activities

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Informed consent/assent[d]	X								
Demographics and medical history	X								
Performance status	X								
Inclusion/exclusion criteria	X								
CCI									
Physical examination	X	A complete physical examination is to be conducted at Screening and EOT only, and as clinically indicated.							
Psychological assessments [f]	X						X		
Vital signs, weight, and height [g]	X	X	X	X	X	X (Cycle 3 only)	X	X	X

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
CBC with differential [h]	X	X (Twice weekly for Safety Run-in only)	X (Twice weekly for Safety Run-in only)	X (Twice weekly for Safety Run-in only)	X		X		
Coagulation [h]	X	As clinically indicated					X		
Blood chemistry [h]	X	X	X	X	X		X		
Serum or urine pregnancy test (WOCBP only) [i]	X	X			X		X	X	X
CCI									
12-lead ECG [k]	X				X (Cycle 3 only)		X		
Dostarlimab administration		X			X				
Niraparib dispensed/collected (administered Day 1 after dostarlimab infusion)		X			X		X (Collection only)		

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Tumour assessment: CT or MRI[l,m]	X[n,o]	Every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first[p]					X[q]		
Tumour assessment: MIBG-SPECT/CT or FDG-PET/CT [m]	X[n,o]	Every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first[p]					X[q]		
Bone marrow assessment	X[s]	If positive at baseline, every 9 weeks (every 63 [±7] days) following the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter, or more frequently if clinically indicated, until documented PD, the start of alternative anticancer treatment, or discontinuation from overall study participation (e.g., death, participant's request, or participant is lost to follow-up), whichever comes first. . Required for all participants to confirm disease response					X[q]		
CCI [redacted]									
AE monitoring [u]	X	X	X	X	X	X	X	X	X

Protocol Activity	Screening Period	Treatment Period					EOT Visit [a,b]	Safety FUP Visit (30 [+7] Days Post-Treatment)[b]	FUP Assessment Period (Every 90 [±14] Days Post-Treatment) [c]
Study treatment cycle		**Cycles 1-2**			**Cycles 3+**				
Cycle week		**1**	**2**	**3**	**1**	**2**			
Study day	**-28 to -1**								
Study visit window (days within cycle)		**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**
Procedure									
Prior and concomitant medications and nondrug treatments	X	Medications and nondrug treatments will be monitored for study purposes from Screening to at least 30 days following the last dose of study treatment							
Blood sample for dostarlimab PK and/or ADAs and neutralising antibodies [v,w]		X	X (Cycle 1 only)		X (predose, Cycles 4 and 6, and every 6 cycles thereafter)		X	X	X
Blood sample for niraparib PK [w,x]		X (Cycles 1 and 2 only)	X (Cycle 1 only)						
CCI									
Alternative anticancer treatment assessment							X	X	X

Abbreviations: ADA=antidrug antibody; AE=adverse event; AESI=adverse event of special interest; ALP=alkaline phosphatase; BP=blood pressure; CCI ; CBC=complete blood count; CNS=central nervous system; CR=complete response; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; EOT=End of Treatment; FDG-PET/CT=fluorodeoxyglucose-positron emission tomography/computed tomography; FUP=follow-up; G-CSF=granulocyte-colony stimulating factor; HbcAb=hepatitis B core antibody; HbsAg=hepatitis B surface antigen; HCVAb=Hepatitis C virus antibody; INRC=International Neuroblastoma Response Criteria; IV=intravenous; MIBG-SPECT/CT=metaiodobenzylguanidine-single photon emission computed tomography/computed tomography; MRI=magnetic resonance imaging; PD=progressive disease; PET=positron emission tomography; PK=pharmacokinetics; PR=partial response; SAE=serious adverse event; WOCBP=woman of childbearing potential.

a. All participants will undergo an EOT Visit no more than 7 days following the decision to discontinue study treatment for any reason.

b. The Safety FUP Visit and EOT Visit can be combined if both fall within the same window. The Safety FUP Visit is to take place no sooner than 30 days after last dose to permit the protocol-required collection of AEs/SAEs occurring during this 30-day interval. The Safety FUP Visit has a window of +7 days.
c. During the FUP Assessment Period, participants will be followed via clinic visit or telephone contact every 90 (±14) days after the last dose of study treatment for the first year, every 180 (±14) days for the subsequent 2 years, and yearly (±14 days) for an additional 2 years (5 years total), or until the start of alternative antitumour therapy (unless there is an ongoing AE/SAE that must be followed until resolved, stabilised, or otherwise explained), the participant withdraws from the study overall, is lost to follow-up, or dies (whichever occurs earlier).
d. Informed consent/assent must be obtained prior to undergoing any study-specific procedure and may occur prior to the 28-day Screening Period.
e. CCI [redacted]
f. Psychological assessments to be performed as per local standard of care.
g. Vital signs include temperature, blood pressure, heart rate, and respiratory rate. Vital signs will be taken before, every 15 to 30 minutes during, and at the end of every dostarlimab infusion. Throughout the Treatment Period, all vital signs will be monitored at Week 1 of each cycle even if dostarlimab is not administered. In addition, for the first 8 weeks of the Treatment Period (up to and including Cycle 3 Week 2), all vital signs will be monitored at Week 2 and Week 3 of each cycle. Height and weight will be measured at Screening, Day 1 of each cycle, EOT, 30-day Safety Follow-up, and during the FUP Assessment Period.
h. Haematology, coagulation, and chemistry assessments will be performed by local laboratories. Parameters required in this study are listed in the master protocol. Haematology and chemistry assessments must be measured within 7 days prior to Cycle 1 Day 1 to confirm eligibility. Haematology and chemistry must be performed, and results evaluated prior to study treatment administration. Haematology is to be checked twice each week during the first 2 cycles of study treatment for participants enrolled in the Part 2 Safety Run-in and once weekly for participants enrolled in the Part 2 Neuroblastoma Expansion Cohort. Haematology tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the participant's study file, and the results must be entered into the eCRF. If dose interruption or modification is required at any point on study because of haematologic toxicity, weekly blood draws for CBC will be done according to Table 8. Additional haematology or chemistry assessments may be performed according to local standard of care or as clinically indicated. If Cycle 1 Day 1 is no more than 7 days following sample collection for Screening, these samples do not need to be collected again for Cycle 1 Day 1, unless clinically warranted. Additional monitoring for haematology is to be performed after a niraparib dose increase due to a birthday or due to a weight increase that moves participants to a higher CCI [redacted], respectively. Haematology is to be checked twice each week during the first 2 cycles after the niraparib dose increase for participants enrolled in the Part 2 Safety Run-in and once weekly for participants enrolled in the Part 2 Neuroblastoma Expansion Cohort. Blood samples should be collected in order of priority as outlined in Section 8.2.
i. If the participant is a WOCBP, urine or serum pregnancy test will be performed by the local laboratory at the Screening Visit, within 24 hours prior to the first dose of study treatment, on Day 1 of every cycle for the duration of the Treatment Period, at the End of Treatment Visit, at the 30-day Safety Follow-up Visit, and 180 (±14) days after the last dose of study treatment. Pregnancy testing should occur irrespective of prior medical treatment. The results from these tests must be available and negative before study treatment is administered. Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected.
j. CCI [redacted]
k. ECG should be repeated at Cycle 3 Week 1 and EOT, as well as during the Treatment or FUP Periods if clinically indicated.
l. CT scans should be performed with contrast agents unless contraindicated for medical reasons. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such a case, CT will be performed without contrast to evaluate the lung parenchyma. If MRI is used to follow-up bone lesion(s), it must be performed prior to any treatment that may affect bone marrow cellularity (eg, G-CSF). PET/CT may be used according to INRC guidelines with full-dose diagnostic CT and as clinically indicated.

m. The same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant. Clinical assessment of superficial lesions should be carried out on the same date as the imaging studies or no later than 3 days thereafter and must be recorded in the participant's eCRF.
n. Participants must have a baseline tumour assessment (CT or MRI) of the chest, abdomen, pelvis, and any additional sites as clinically indicated within 28 days prior to the first dose of study treatment. Participants with neuroblastoma must also have a baseline tumour assessment via MIBG-SPECT/CT or FDG-PET/CT within 42 days prior to the first dose of study treatment. A baseline IV contrast-enhanced brain MRI (preferred) or IV contrast-enhanced CT scan (acceptable only if MRI contraindicated), is required for participants with previously treated brain metastases. Participants with previously treated brain metastases may participate under the conditions detailed in Exclusion Criterion 7.
o. Radiologic assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations, if all of the following conditions are met:
    (1) the CT or MRI tumour assessments were obtained within 28 days prior to the first dose of study treatment/the MIBG-SPECT/CT or FDG-PET/CT tumour assessments were obtained within 42 days prior to the first dose of study treatment
    (2) the assessments were performed using the method requirements outlined in INRC,
    (3) the same imaging technique/modality must be used to follow identified lesions throughout the study for a given participant, and
    (4) appropriate documentation indicating that these radiologic tumour assessments were performed as standard of care is available in the participant's source notes.
p. Tumour assessments of sites involved by disease at baseline, and of any additional sites as clinically indicated will be done postbaseline, as will MIBG-SPECT/CT or FDG-PET/CT tumour assessments (see Table 4). Tumour assessments will be conducted as per the schedule outline in Table 3. Tumour assessments should be scheduled using the date of the first dose of study treatment as the reference date for all time points and are not to be scheduled based on the date of the previous imaging time point. Imaging assessment delay to conform to study treatment delay is not permitted.
q. Participants who have already demonstrated documented PD as per INRC do not need to have tumour assessments repeated at the EOT Visit or during the Post-Treatment FUP. Participants who do not have documented PD at time of study treatment discontinuation will continue to undergo tumour assessments on their original schedule (i.e., every 9 weeks [every 63 ±7 days] from the start of study treatment for the first 12 months and then every 12 weeks [every 84 ±7 days] thereafter, until documented PD, start of alternative anticancer treatment, or discontinuation from overall study participation [eg, death, participant's request, or participant is lost to follow-up], whichever comes first). Participants who have a PR or CR while on treatment and discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.
r. (Footnote intentionally left blank.)
s. Bone marrow assessments obtained per the standard of care prior to enrolment into the study do not need to be repeated and are acceptable to use as baseline evaluations if obtained within 28 days prior to the first dose of study treatment.
t. Only at Cycle 1 Week1 and Cycle 1 Week 2 for participants who receive CCI niraparib tablets and those who receive CCI
u. AEs will be collected until 30 days after the last dose of study treatment. SAEs will be collected until 90 days after the last dose of study treatment (or to a minimum of 30 days after the last dose of study treatment if the participant starts alternative anticancer treatment). However, any SAEs assessed as related to study participation or related to study treatment will be recorded through the FUP Assessment Period. AESIs must be recorded on the eCRF. AESI collection periods are described in the master protocol. Any pregnancies that occur in female participants within 180 days after the last dose of study treatment or in partners of male participants within 90 days after the last dose of study treatment are to be reported as described in the master protocol. Pregnancies occurring more than 180 days after last dose of study treatment with an associated SAE (considered causally related to the study treatment by the Investigator) will follow the SAE reporting requirements. All AEs and SAEs will be followed, regardless of start of alternative anticancer therapy, until the event is resolved, stabilised, or otherwise explained; or until the participant has withdrawn consent to the study overall, is lost to follow-up (as defined in Section 7); or has died.
v. Blood samples (single sample for all analytes) for serum dostarlimab PK and/or ADA and neutralising antibodies (NAb) will be collected from participants during Cycle 1 at the following time points relative to the start of the dostarlimab infusion: Cycle 1 Day 1 at Predose (PK, ADA, and NAb) and 1±0.5 hours postdose (PK only), Cycle 1 Day 8 at

168±12 hours postdose (PK, ADA and NAb), and predose on Cycle 2 Day 1 (predose sample must be collected within 12 hours prior to infusion) (PK, ADA and NAb). Blood samples for serum dostarlimab PK, ADA, and NAb will also be collected at the following time periods: Predose in Cycles 4 and 6, every 6 cycles thereafter up to 2 years, and the EOT Visit. In addition, blood samples for serum dostarlimab ADA and NAb will be collected at the Safety Follow-up Visit (30 days post-treatment) and at the first Follow-up Visit (90 days post-treatment). PK, ADA, and NAb samples will be drawn at the same time points and in the same collection, except as noted.

w. The maximum blood volume for each sample for PK, ADA, and NAb) and exploratory biomarker assessments is 0.8 mL/kg, and the maximum total blood volume allowed for PK, ADA, and NAb, and exploratory biomarker assessments is 1.8 mL/kg per 3-week treatment cycle. Blood samples should be collected in order of priority as outlined in Section 8.2.

x. Blood samples for plasma niraparib and M1 metabolite concentration analyses (single sample for both analyses) will be collected from participants during Cycle 1 Day 1 at 2.5 and 7 hours after the first dose of niraparib, predose on Cycle 1 Day 8, predose on Cycle 2 Day 1, and Cycle 2 Day 1 at 5 hours after niraparib dose. Additional niraparib PK sampling is to be performed after a niraparib dose increase due to a birthday or after a dose modification due to a weight increase or decrease. (These additional PK samples will be taken on Day 1 in the first cycle after the dose change at 2.5 and 7 hours postdose, predose on Day 1 of the second cycle after the dose change, and at 5 hours after the niraparib dose on Day 1 of the second cycle after the dose change.) Note: Predose samples must be collected within 2 hours prior to dosing; Cycle 1 Day 1 2.5 hour samples must be collected at the scheduled time ±0.5 hour and other samples must be collected at the scheduled time ±2 hours.

y. CCI [redacted] Blood samples should be collected in order of priority as outlined in Section 8.2.

Table 4: Tumour Assessment Flowchart

Tumour Assessment	Screening Period	Treatment Period	Confirmation of Response[a]	Post-Treatment Follow-up
CT or MRI of chest, abdomen, pelvis, and any additional sites as clinically indicated	Required	Required, including site of any other tumour lesions identified at baseline and of any additional sites as clinically indicated	Required, including site of any other tumour lesions identified at baseline	If PD has been documented: Not required If PD has not been documented: Required, including sites of any other tumour lesions identified at baseline
Brain scan (IV contrast-enhanced MRI [preferred] or IV contrast-enhanced CT scan)	Required for participants with previously treated brain metastases	Not required unless clinically indicated	Required if baseline scan was positive	Not required unless clinically indicated
MIBG-SPECT/CT for participants with MIBG-avid tumours or FDG-PET/CT as the alternative modality for participants whose tumours do not concentrate MIBG	Required	Required	Required	If PD has been documented: Not required If PD has not been documented: Required
Clinical assessment of superficial lesions	Required	Required for sites of tumour lesions identified at baseline and any additional sites as clinically indicated	Required for sites of tumour lesions identified at baseline	Required for sites of tumour lesions identified at baseline, unless PD has been documented elsewhere

Tumour Assessment	Screening Period	Treatment Period	Confirmation of Response[a]	Post-Treatment Follow-up
Bone marrow aspirate and biopsy	Required	Required for participants with bone marrow involvement at Screening	Required for all participants	If PD has been documented: Not required If PD has not been documented: Required for participants with bone marrow involvement at Screening

Abbreviations: CT=computed tomography; EOT=End of Treatment; FDG-PET/CT=fluorodeoxyglucose-positron emission tomography/computed tomography; MIBG-SPECT/CT=metaiodobenzylguanidine-single photon emission computed tomography/computed tomography; MRI=magnetic resonance imaging; PD=progressive disease.
Note: See Table 3 for detailed guidance on tumour assessment procedures.

a. Participants who have a PR or CR while on treatment and discontinue treatment prior to the next disease assessment must have all appropriate follow-up disease assessments to confirm the observed response no sooner than 4 weeks (28 days) after the first observation.

2. INTRODUCTION

An introduction to the overall study is provided in the master protocol. The objective of the Part 2 Safety Run-in Cohort is to evaluate the safety, tolerability and preliminary efficacy of the [redacted]
The objective of the Expansion Cohort of participants with neuroblastoma (the "NB Cohort") is to assess the antitumour activity of the combination of niraparib and dostarlimab, assessed primarily by objective response rate (ORR) using International Neuroblastoma Response Criteria (INRC) in paediatric participants.

2.1. Background

2.1.1. Background of Niraparib

Overall clinical experience with niraparib is summarised in the master protocol.

2.1.2. Background of Dostarlimab

Overall clinical experience with dostarlimab is summarised in the master protocol.

2.1.3. Rationale for Synergy Between PARP Inhibitors and Immune Checkpoint Inhibitors

The rationale for synergy between poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors and immune checkpoint inhibitors is summarised in the master protocol.

2.2. Rationale for Tumour Type

[redacted]

2.3. Rationale for Current Study

The rationale for the current study is provided in the master protocol.

2.4. Benefit Risk Assessment

The overall benefit risk assessment and dose justification is described in the master protocol.

3. STUDY OBJECTIVES AND PURPOSE

The cohort-specific objectives for this study are defined in Table 5 as follows:

Table 5: Objectives and Endpoints for Study 213406 Neuroblastoma Cohort

Objectives	Endpoints
Part 2 Safety Run-in	
Primary	
Assessment of safety and tolerability of the CCI [redacted] by assessing DLT and Grade ≥3 thrombocytopenia AEs in paediatric participants	• Assess the incidence of DLTs in the Part 2 Safety Run-in for the DLT-evaluable Population. • Assess the incidence of Grade ≥3 thrombocytopenia AEs in the Part 2 Safety Run-in for the DLT-evaluable Population.
Secondary	
Evaluation of measures of anticancer activity, including ORR, DOR, DCR, and PFS in paediatric participants	ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma. DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment or death (whichever occurs first). DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment. PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment, or death from any cause (whichever occurs first).
To evaluate safety of the combination of CCI [redacted] in paediatric participants	Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.

Objectives	Endpoints
To characterise the PK of niraparib in paediatric participants	Niraparib concentrations; PK parameters of niraparib, if appropriate.
Part 2 Expansion	
Primary	
Assess the antitumour activity of the combination of CCI [redacted], assessed primarily by ORR (using INRC) in paediatric participants	ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using INRC.
Secondary	
Evaluation of additional measures of anticancer activity including DOR, DCR, and PFS in paediatric participants	DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC based on Investigator assessment or death (whichever occurs first). DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC based on Investigator assessment. PFS is defined as the time from the date of the first dose of study treatment to the first documented PD as determined by INRC based on Investigator assessment, or death from any cause (whichever occurs first).
Evaluation of the safety of the combination of CCI [redacted] in paediatric participants	Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
Characterisation of the PK of the combination of niraparib and dostarlimab in paediatric participants	Niraparib and dostarlimab concentrations; PK parameters of niraparib and dostarlimab, if appropriate.
Assessment of the immunogenicity of dostarlimab in paediatric participants	Rate and extent of ADAs to dostarlimab.
CCI [redacted]	

Objectives	Endpoints
Exploratory	
CCI [redacted]	

Abbreviations: ADA=antidrug antibody(ies); AE(s)=adverse event(s); BOR=best overall response; CR=complete response; CCI [redacted]; DCR=disease control rate, DLT=dose limiting toxicity; DOR=duration of response; INRC=International Neuroblastoma Response Criteria; imAE=immune-mediated adverse event; ORR=objective response rate; CCI [redacted]; PD=progressive disease; PD-1=programmed cell death protein 1; PFS=progression-free survival; PK=pharmacokinetic(s); PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SAE(s)=serious adverse event(s); SoA=schedule of activities; TEAE(s)=treatment-emergent adverse event(s); CCI [redacted].

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The overall study design is described in the master protocol.

CCI

[redacted]

The Part 2 study design is illustrated in Figure 1.

CCI

[redacted]

CCI [redacted]

Once all participants in the Safety Run-in have been observed for ≥42 days, all available data from the Part 2 Safety Run-in together with all data previously collected under Protocol Amendment 04 and earlier, will be reviewed by the study DEC and Data Review Committee (DRC) before additional participants on Part 2 are enrolled.

Following the Safety Run-in, if the CCI [redacted] is deemed safe, up to 30 evaluable participants may enrol in the Part 2 Cohort Expansion for neuroblastoma, inclusive of any eligible participants with neuroblastoma treated in the Part 2 Safety Run-in. Enrolment into the Part 2 Cohort Expansion will be conducted according to a Simon's 2-stage optimal design in which ≥2 of the first 10 evaluable participants must experience an objective tumour response (as assessed by the Investigator using INRC) before accrual of the remaining 20 participants.

CCI [redacted]

CCI [redacted]

General study conduct is described in the master protocol. CCI [redacted]

4.1.1. Dose Limiting Toxicity

The DLT and thrombocytopenia toxicities observation period for the Safety Run-in is 42 days following the initiation of study treatment (i.e., approximately the first 2 treatment cycles) in Part 2.

A participant will be considered unevaluable for DLT assessment if, for reasons other than DLT, the participant does not complete the DLT observation period or receives <80% of the intended niraparib dose (e.g., missed 9 or more doses; reason for missed doses may include, but is not limited to, noncompliance) or <2 infusions of dostarlimab.

A participant will be considered unevaluable for thrombocytopenia events if, for reasons other than thrombocytopenia, the participant does not complete the DLT observation period or receives <80% of the intended niraparib dose (e.g., missed 9 or more doses; reason for missed doses may include, but is not limited to, noncompliance) or <2 infusions of dostarlimab.

Participants considered unevaluable may be replaced after consultation between the Sponsor and Investigator.

A participant may continue on study treatment following a DLT or a thrombocytopenia event if the Investigator determines doing so is in the best interest of the participant, after discussion by the Investigator with the GSK Medical Monitor, and after appropriate recovery from the DLT by the participant.

DLT is defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related Grade 4 nonhaematologic clinical (nonlaboratory) AE
- any treatment-related Grade 3 nonhaematologic clinical (nonlaboratory) AE not resolving to Grade ≤1 within 48 hours of initiating optimal medical intervention
- any treatment-related Grade 3 or 4 nonhaematologic laboratory abnormality if any of the following also occur:
  - the abnormality leads to hospitalisation.
  - the abnormality persists for ≥7 days from the time of AE onset and participant is symptomatic from the AE and/or requires intervention.
- any treatment-related haematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for >7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding or requiring platelet transfusion.
  - Grade 4 neutropenia persists for >7 days, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥72 hours.
  - Grade 4 anaemia or Grade 3 anaemia requiring blood transfusion.
- any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2
- any treatment-related Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks
- any treatment-related Grade ≥2 immune-related endocrine toxicity that requires hormone replacement, except Grade 2 thyroiditis or thyroid dysfunction
- any treatment-related Grade 2 colitis or diarrhoea that persists for ≥7 days without resolution to Grade ≤1 despite adequate steroid therapy

- any Grade 3 or 4 imAE that does not resolve to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy
- Grade 3 or higher infusion-related reaction
- any grade of hemophagocytic lymphohistiocytosis
- any grade of Posterior Reversible Encephalopathy Syndrome (PRES)
- any treatment-related Grade 5 AE

Thrombocytopenia events are defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related toxicity defined as any of the following:
  - Grade 3 Grade 4 thrombocytopenia

4.2. Number of Participants

Safety Run-in: approximately 8 DLT-evaluable participants in total across osteosarcoma (Part 2A) and neuroblastoma (Part 2B).

Part 2 Expansion: approximately 30 participants with neuroblastoma are planned for enrolment in this cohort (including eligible participants with neuroblastoma from the Safety Run-in). See Section 9.1 for eligibility requirements for enrolment of Safety Run-in participants in the Part 2 Cohort Expansion.

4.3. Treatment Assignment

All participants enrolled in this cohort will receive niraparib in combination with dostarlimab as described in Section 4.1.

4.4. Dose Adjustment Criteria

4.4.1. Dose Adjustment Criteria for Age and Weight

CCI [redacted]

4.4.2. Dose Adjustment for Adverse Events

Adverse reactions should be managed with dose reduction, interruption of treatment, or dose discontinuation.

All dose reductions, treatment delays (including any missed doses) and discontinuations, and the reason for such modifications should be recorded in the eCRF.

It should be noted that required treatment discontinuation of either niraparib or dostarlimab will result in study treatment discontinuation of both treatments.

4.4.3. Niraparib

The recommended dose modifications for adverse reactions should be followed as listed in Table 6, Table 7, and Table 8. Following a dose reduction, participants should not subsequently have dose re-escalated unless a discussion with the GSK Medical Monitor has occurred.

Following 2 dose reductions, participants will not be allowed to further dose reduce, and study treatment should be discontinued. In addition, study treatment should be discontinued for selected AEs that persist beyond 28 days, as noted in Table 7 and Table 8.

CCI

[redacted]

Table 7: Niraparib Dose Modifications for Nonhaematologic Adverse Reactions

NCI CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	• Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6.
NCI CTCAE Grade ≥2 adverse reaction of PRES	• Discontinue study treatment for participants

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; PRES=Posterior Reversible Encephalopathy Syndrome.

There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with PRES. PRES is a rare neurologic disorder that can present with signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

Table 8: Niraparib Dose Modifications for Haematologic Adverse Reactions

Weekly blood draws for CBC will be monitored until the adverse reaction resolves; after resuming niraparib, weekly blood draws for CBC will be required for an additional 4 weeks (28 days) after the adverse reaction has been resolved to the specified levels, after which monitoring at Week 1 of each cycle may resume (**Table 3**).	
Platelet count <100 000/µL	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL. Resume niraparib at the same or lower dose per Table 6. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at the same or reduced dose per Table 6. • If nadir platelet count was <75 000/µL, niraparib dose should be reduced per Table 6.
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 000/µL. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6
Neutrophil <1000/µL or Haemoglobin <8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1000 µL or haemoglobin returns to ≥8 g/dL. • For those adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the GSK Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6
Haematologic adverse reaction requiring transfusion	• For participants with platelet count ≤10 000/µL, platelet transfusion should be considered. If there are other risk factors, such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Red blood cell transfusion(s) may be given at the discretion of the Investigator. • Resume niraparib at a reduced dose per Table 6.
MDS/AML	Any suspected case of MDS/AML reported while a participant is receiving treatment or followed for post-treatment assessments must be referred for evaluation to a local haematologist to perform bone marrow aspirate and biopsy as per local standards of practice. The study site must receive a copy of the haematologist's report of aspirate/biopsy findings, which must include a classification according to the WHO, and other sample testing reports related to MDS/AML. If a diagnosis of MDS/AML is confirmed by a haematologist, the participant must permanently discontinue study treatment.

For clinical situations not covered by this dose modification guidance, the Investigator must contact the GSK Medical Monitor.

4.4.4. Dostarlimab

Dostarlimab dose adjustment criteria are presented in the master protocol.

4.5. Criteria for Study Termination

Criteria for study termination are described in the master protocol.

4.6. End of Study Definition

End of study definition is described in the master protocol.

4.7. Study Conduct

4.7.1. Procedures by Visit

Standard of care tests/procedures, including laboratory assessments, ECG, physical examination, vital signs, height, weight, and performance status, performed before the enrolment into the study can be used as part of the Screening assessments as long as the tests/procedures are performed within the visit window indicated in Table 3. Local laboratory assessments (chemistry, haematology) must be performed and results reviewed no more than 7 days prior to administration of the first dose of study treatment, as indicated in Table 3. Tumour assessment CT or MRI, and MIBG-SPECT/CT or FDG-PET/CT scan obtained per the standard of care prior to the first dose of study treatment (within 28 days for CT or MRI and 42 days for MIBG-SPECT/CT or FDG-PET/CT) do not need to be repeated and are acceptable to use as baseline evaluations if the conditions presented in Section 8.1.2.1 of the master protocol are met. Source documents must clearly identify the standard of care tests/procedures that are used for Screening, and the results of these tests/procedures must be entered in the eCRF. Table 3 details which procedures are performed at each visit.

4.7.2. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic

Due to the significant challenges that currently face the healthcare system and patients due to Coronavirus Disease 2019 (COVID-19), as well as the potential for enduring or additional quarantine measures, the following guidance is being provided in this protocol. In the spirit of global diversity in the COVID-19 pandemic and its impact on healthcare in each individual country as well as the recently issued guidance by several regulatory authorities, the autonomy of each investigative site to assess the benefit/risk for their patients participating in clinical studies should be maintained.

Prior to utilisation of any of the measures outlined in this section, discussion and approval must be obtained from Sponsor/contract research organisation.

It is expected that sites participating in clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the SoA (Table 3). The use of local laboratories and local radiology centres to reduce the need

for a participant to come into the clinic are supported, if deemed necessary for the well-being of the participant. These local facilities should be added to regulatory documents, as required.

Additionally, regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring programs to maintain oversight of clinical sites. Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor/contract research organisation.

General rules for participants with limited possibility to travel are as follows:

- If possible, replace in-person visits with phone contact or alternative location for assessment (eg, local laboratories and imaging centres).

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Participant Inclusion Criteria

Participants will be eligible for the Safety Run-in and Neuroblastoma Expansion Cohort of Part 2 if all of the following criteria are met:

1. CCI [redacted].
2. Participant with neuroblastoma has measurable/evaluable disease by International Neuroblastoma Response Criteria (INRC) at screening. Participants with recurrent/relapsed bone metastasis that is metaiodobenzylguanidine (MIBG)-positive (or FDG-positive, for MIBG-nonavid tumours) as only site of disease are eligible.

CCI [redacted]

5. Performance status must be ≥60% on the Karnofsky scale for participants >16 years of age and ≥60% on the Lansky scale for participants ≤16 years of age.

   Note: Neurologic deficits in participants with brain metastases must have been stable for at least 7 days prior to study enrolment. Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance status.

6. Participant has adequate organ function, defined as follows:

   Note: The participant must not have received blood transfusion, growth factors, or platelet stimulating agents in the 14 days prior to providing a sample for haematologic analysis nor erythropoietin in the prior 6 weeks.

   a. absolute neutrophil count ≥1000/µL
   b. platelets ≥100 000/µL

c. haemoglobin ≥8 g/dL or ≥5.0 mmol/L
d. creatinine≤1.5×upper limit of normal (ULN) for age or calculated creatinine clearance or radioisotope glomerular filtration rate ≥60 mL/min/1.73m^2
e. total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 × ULN
f. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case AST and ALT must be ≤5 × ULN
g. international normalised ratio or prothrombin time (PT) ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
h. activated PTT ≤1.5 × ULN unless the participant is receiving anticoagulant therapy, as long as PT or PTT is within therapeutic range of intended use of anticoagulants

7. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   a. Is not a woman of childbearing potential (WOCBP).

   Or

   b. Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 3 of the master protocol, from the Screening Visit through at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
   c. A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours prior to the first dose of study treatment and irrespective of prior medical treatment.

   Additional requirements for pregnancy testing during and after the Treatment Period are located in the master protocol.

   The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. A male participant of reproductive potential is eligible to participate if he agrees to the following starting with the first dose of study treatment through at least 90 days (a spermatogenesis cycle) after the last dose of study treatment:

   a. refrain from donating sperm

   plus, either:

   b. be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

   or

   c. must agree to use a male condom and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may

break or leak, when having sexual intercourse with a WOCBP who is not currently pregnant

9. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.
10. CCI [redacted]

5.2. Participant Exclusion Criteria

Participants will not be eligible for study entry if any of the following criteria are met:

1. Participation presents unacceptable risk to the prospective participant based on the Investigator's judgement.
2. Participant has known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.
3. Participant has received prior therapy with an anti-PD-1, anti-programmed cell death-ligand 1, anti-programmed cell death-ligand 2, anticytotoxic T-lymphocyte-associated antigen-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received dostarlimab).
4. Participant has had prior treatment with a known PARP inhibitor (with the exception of participants rolling over from Part 1 of the study: these participants are allowed to have received niraparib).
5. Participant has a known history of myelodysplastic syndrome or acute myeloid leukaemia.
6. Participant has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying antirheumatic drugs, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
7. Participant has known active central nervous system (CNS) metastases, carcinomatous meningitis, or both. Note: Participants with previously treated brain metastases may

participate provided they are clinically stable and have no evidence of new, enlarging, or progressing brain metastases (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks (28 days) prior to the first dose of study treatment. In addition, the participant must not have been using steroids for at least 7 days prior to the first dose of study treatment. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.

8. Participant had a known additional (second primary) malignancy that progressed or required active treatment within the last 2 years.
9. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining assent/consent).
10. Participant has a condition (such as transfusion-dependent anaemia or thrombocytopenia), requirement for therapy, or laboratory abnormality that might confound the study results or interfere with the participant's participation for the full duration of the study treatment.
11. Participant is pregnant, breastfeeding, or expecting to conceive within the projected duration of the study, starting with the Screening Visit through 180 days after the last dose of study treatment.

    No data are available regarding the presence of dostarlimab or niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from dostarlimab and/or niraparib, female participants should not breastfeed during treatment with dostarlimab and/or niraparib and for at least 4 months after the last dose of dostarlimab or at least 30 days after the last dose of niraparib, whichever is longer.
12. Participant has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
13. Participant has a known history of HIV (type 1 or 2 antibodies).
14. Participant has documented presence of HbsAg and/or HbcAb at Screening or within 3 months prior to first dose of study intervention. Participants with a negative HbsAg and positive HbcAb result are eligible only if HBV DNA is negative (Appendix 12 of the master protocol),
15. Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc.

16. Participant has had any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer therapy and that persisted >4 weeks (28 days).
17. Participant has not recovered (ie, to Grade ≤1 or to baseline) from prior systemic therapy-induced AEs. Note: Participants with alopecia, hearing impairment, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/or Grade ≤2 neutropenia are an exception to this criterion and may qualify for participation in the study.
18. Participant had toxicity related to prior immunotherapy that led to treatment discontinuation.
19. Participant had treatment with systemic anticancer therapy (investigational agent or device, or approved chemotherapy, targeted therapy, immunotherapy, or other systemic therapy) within the 3 weeks or 5 half-lives, whichever is shorter prior to the first dose of study treatment, radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment, or any radiation therapy within 1 week prior to the first dose of study treatment.
20. Participant has not recovered adequately from AEs or complications from any major surgery prior to starting study treatment.
21. Participant has received a live vaccine within 30 days of planned start of study treatment.
22. Participant has clinically significant cardiovascular disease (eg, significant cardiac conduction abnormalities, uncontrolled hypertension, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, and history of cerebrovascular accident) within 6 months of enrolment.
23. Participant has heart rate-corrected QT interval prolongation at Screening >450 msec or >480 msec for participants with bundle branch block.

    Notes:
    - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine read or manually over read.
    - The specific formula that will be used to determine eligibility and discontinuation for an individual participant must be determined prior to initiation of the study and used consistently for eligibility and study assessments.
24. Participant has received a solid organ transplant.
25. Participant has a documented presence of HCV antibody at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with a positive HCV antibody test result due to prior resolved disease can be enrolled, only if a confirmatory HCV RNA test is negative and the participant otherwise meets all entry criteria.
26. Participant has a documented presence of HCV RNA at Screening or within 3 months prior to first dose of study intervention. NOTE: The HCV RNA test is optional and participants with negative HCV antibody test are not required to undergo HCV RNA testing as well.

5.3. Lifestyle Considerations

Cases of photosensitivity have been reported for patients on niraparib treatment. Participants must be informed on measures to decrease exposure to ultraviolet light, such as minimising time in direct sunlight unless wearing hats and long-sleeves and application of sun protection creams.

5.4. Screen Failures

The definition of a screen failure is provided in the master protocol.

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

CCI [redacted]

Niraparib will be dispensed to participants on Day 1 of every 21-day treatment cycle.

The niraparib dosing regimens under Protocol Amendment 05 are shown the master protocol.

CCI [redacted]

Details about the investigational products are provided in Table 9.

Table 9: Investigational Products

	Investigational Product		
Intervention name	Niraparib	Niraparib	Dostarlimab
Type	Drug	Drug	Biologic
Dosage form	CCI [redacted]		
Unit dose			
Route of administration			
Use	IMP	IMP	IMP
Authorised AxMP/ Unauthorised AxMP	Not applicable	Not applicable	Not applicable
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Physical description (Packaging and Labelling; see Section 6.2.1)	CCI [redacted]		
Dose level(s)	See master protocol	See master protocol	See master protocol
Manufacturer	WuXi STA (WuXi), China (DS, DP) Dishman, India (DS) Corden, Colorado, US (DS) Mayne Pharma, Raleigh, North Carolina, US (DP) Siegfried, Switzerland (DS)	WuXi STA (WuXi), China (DS, DP) Corden, Colorado, US (DS) Dishman, India (DS) Siegfried, Switzerland (DS)	WuXi Biologics (WuXi), Wuxi, China (DS) Ajinomoto Althea (Aji), San Diego, California, US (DP)

Abbreviations: AxMP = auxiliary medicinal product; DP=drug product; DS=drug substance; IMP = investigational medicinal product; IV=intravenous; Non-IMP = non-investigational medicinal product; CCI [redacted]; US=United States.

Further details on the study interventions are provided in the master protocol and respective IBs.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Treatment Packaging and Labelling

Overall study treatment packaging and labelling are described in the master protocol.

6.2.2. Study Treatment Storage

Study treatment storage is described in the master protocol.

6.2.3. Administration

Details on the administration of the study treatments can be found in the Pharmacy Manual. A summary is provided in the master protocol.

6.2.4. Study Treatment Accountability

Study treatment accountability is described in the master protocol.

6.2.5. Study Treatment Handling and Disposal

Study treatment handling and disposal are described in the master protocol.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomised, open-label study.

6.4. Study Treatment Compliance

Overall study treatment compliance information is presented in the master protocol. Study treatment (dostarlimab and niraparib during dostarlimab infusion visits) will be administered by investigational site personnel at investigational sites.

6.5. Dose Modification

Dose reductions for dostarlimab are not permitted while participant is being treated on study. Dosing may be held in the event of an AE which may be deemed related to treatment. If 2 or more consecutive dostarlimab doses are held, Investigator must notify the GSK Medical Monitor for approval to continue treatment of the participant on study.

Refer to Section 4.4 for full dose modification guidance for niraparib and Section 4.7 in the master protocol for full dose modification guidelines for dostarlimab.

6.6. Treatment of Overdose

This information is described in the master protocol.

6.7. Concomitant Therapy

Details on the definition and recording of concomitant medications are provided in the master protocol.

6.7.1. Rescue Medications

Participants should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including but not limited to the items outlined in Section 6.8.1 of the master protocol.

6.7.2. Prohibited Medications

Known prior medications that exclude a participant from participating in this cohort are described in the exclusion criteria (see Section 5.2).

Medications prohibited in the overall study are provided in the master protocol.

6.7.3. Other Study Restrictions

Other study restrictions are provided in the master protocol.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

Guidance on discontinuation of study treatment is described in the master protocol.

7.1.1. Liver Chemistry Stopping Criteria

Specific guidance on liver chemistry stopping criteria is described in the master protocol in Section 7.1.1 and Appendix 8. Guidance on drug restart or rechallenge following liver safety events, if applicable, is included in Appendix 9 of the master protocol.

7.1.2. QTc Stopping Criteria

Guidance on QTc stopping criteria is described in the master protocol.

7.2. Withdrawal of Consent

Procedures to be followed in cases of consent withdrawal are presented in the master protocol.

7.3. Participant Discontinuation/Withdrawal from the Study

Examples of reasons for discontinuing study treatment or study are applicable across cohorts and are presented in the master protocol.

Guidance on discontinuation of participants from the study, including required actions for participants lost to follow-up, is provided in the master protocol.

7.4. Lost to Follow-Up

Guidance on required actions for participants lost to follow-up is provided in the master protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Assessment of Efficacy

The timing of radiologic evaluations and details regarding the evaluation of tumour response for both the Part 2 Safety Run-in and the Part 2 Neuroblastoma Cohort Expansion are provided in Table 3 and in the master protocol. Participant scan data are not routinely collected in this study; however, such data may be requested under special circumstances, such as during investigation of a significant safety event.

8.1.1. Primary Efficacy Endpoint for the Neuroblastoma Cohort Expansion

The primary efficacy endpoint for this cohort will be ORR based on Investigator assessment, defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using INRC.

8.1.2. Secondary Efficacy Endpoints for the Neuroblastoma Cohort Expansion

The secondary endpoints for this cohort will be DOR, DCR, and PFS based on Investigator assessment using INRC.

8.1.2.1. Duration of Response

DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmed CR or PR. Participants who do not experience PD or who die after they have had a response are censored at the date of their last tumour assessment.

8.1.2.2. Disease Control Rate

DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC based on Investigator assessment.

8.1.2.3. Progression-free Survival

PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC based on Investigator assessment, or death from any cause (whichever occurs first). Participants without an event will be censored at the date of the last tumour assessment. Participants without postbaseline assessments will be censored at the date of the first dose.

CCI [redacted]

8.2. Assessment of Safety

Planned time points for all safety assessments are provided in Table 3.

At some timepoints, the protocol may specify that blood samples for clinical care (i.e., clinical chemistry, haematology, pregnancy) and for study-related research (PK, exploratory biomarkers)

be obtained during a single study visit. In the event of concern for excessive blood volume withdrawal sample collection should be prioritised as follows:

1. clinical care
2. niraparib PK
3. dostarlimab PK, ADA, and NAb
4. CCI [redacted]

8.2.1. Safety Parameters

Safety parameters for this study are described in the master protocol.

8.3. Adverse Events and Serious Adverse Events

Definitions and guidance on AEs and SAEs are provided in the master protocol.

8.4. Pharmacokinetics, Immunogenicity, and Biomarkers

Blood samples to assess niraparib PK, dostarlimab PK, and dostarlimab antidrug antibodies (ADAs) and neutralising antibodies (NAb) will be collected from all participants pre- and postdose at the time points specified in Table 3. CCI [redacted]

Additional details concerning PK and immunogenicity sample collection are provided in the master protocol.

Sample collection should be prioritised as outlined in Section 8.2.

CCI [redacted]

CCI

[redacted]

8.6. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

An overall description of the statistics for this study is provided in the master protocol. Additional details are provided in the Statistical Analysis Plan.

9.1. Sample Size Determination

Part 2 Safety Run-in

The statistical gating to initiate Part 2 Cohort Expansion will be based on minimum of 8 DLT-evaluable participants for DLTs across osteosarcoma and neuroblastoma. When 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia AEs are observed, the study will continue to Part 2 Cohort Expansion. When 3 or more DLTs are observed, the study may not continue to Part 2 Cohort Expansion. When 2 or less DLTs and 3 out of 8 Grade ≥3 thrombocytopenia AEs are observed, the study may be paused for data review. If there is a differential in the DLT-evaluable number of participants to 8 for either endpoint, other criteria may apply and will be specified in the SAP. This will be the primary guideline for the dose recommendations; the totality of data will be taken into account. The probability of initiating Part 2 Cohort Expansion and the probability of pausing for data review are presented in the table below for 8 DLT-evaluable participants, assuming a weak correlation of 0.15 between the 2 endpoints.

True DLT Rate	True Grade ≥3 Thrombocytopenia Rate	Probability of Initiating Part 2 Cohort Expansion (2 or Less DLTs and 2 or Less Grade ≥3 Thrombocytopenia Events Observed Out of 8 DLT-evaluable Participants)	Probability of Pausing for Data Review (3 Grade ≥3 Thrombocytopenia Events and 2 or Less DLTs Observed Out of 8 DLT-evaluable Participants)
0.25	0.25	49%	13%
0.30	0.25	40%	10%
0.30	0.30	32%	13%
0.35	0.35	21%	11%
0.45	0.45	6%	6%

Part 2 Cohort Expansion

The sample size for this cohort is based on a Simon's 2-stage optimal design, with a 1-sided alpha of 0.05 and a minimum power of 80%. The null hypothesis is ≤10% ORR, and the alternative hypothesis is ≥30% ORR. A futility analysis will be performed after the initial assessment of response for 10 evaluable participants in the cohort. If, among the 10 mITT participants in the cohort, at least 2 participants have objective responses (CR or PR), an additional 19 mITT participants will be enrolled. If 6 or more participants out of the 29 participants enrolled have objective responses, the null hypothesis will be rejected. The required sample size of 29 is based on the modified Intent-to-Treat (mITT) Population. The total sample size to be enrolled is planned at approximately 30 in case of the potential lack of sufficient participants in the mITT Population. For consideration of futility, those Part 1 participants who satisfy the inclusion and exclusion criteria of Part 2 Cohort Expansion, satisfy the mITT Population definition, and are treated at the dose used in Part 2 Cohort Expansion will be

included in the Part 2 Cohort Expansion efficacy analysis and will be counted in the required original Part 2 Cohort Expansion sample size. Under Protocol Amendment 05, neuroblastoma Safety Run-in participants who satisfy the mITT Population definition and are treated at the dose used in the Part 2 Cohort Expansion will also be included in the Part 2 Cohort Expansion efficacy analysis and will be counted in the required Part 2 Cohort Expansion sample size. The software for the sample size calculation is PASS 2019 (NCSS).

9.2. Analysis Populations

For the purposes of analysis, the following analysis sets are defined as follows in Table 10.

Table 10: Analysis Sets

Participant Analysis Set	Description
DLT-evaluable	The DLT-evaluable Population consists of participants in Part 2 Safety Run-in who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT for DLT endpoint (or Grade ≥3 thrombocytopenia AEs for the thrombocytopenia event endpoint).
Safety	The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
Intent-to-Treat (ITT)	The ITT Population includes all participants who receive any study medication and have measurable baseline tumour assessment and/or metaiodobenzylguanidine-positive disease (MIBG) (or FDG-positive disease, for MIBG-nonavid tumours) at baseline.
Modified Intent-to-Treat (mITT)	The mITT Population includes all participants who receive any study medication, have measurable baseline tumour assessment and/or MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid tumours) at baseline, and have at least 1 postbaseline tumour assessment.
Per-Protocol	The Per-Protocol Population includes all participants in the mITT Population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.
Pharmacokinetic (PK)	The PK Population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK Populations are defined separately for each agent.
Immunogenicity (ADA) Population	The ADA Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

9.3. Statistical Analyses

9.3.1. General Considerations

All analyses will include summary statistics, including number of participants and percentage for categorical variables and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs based on the Clopper-Pearson method will be provided where appropriate (Clopper, 1934). Time-to-event analyses will be performed using Kaplan-Meier methods.

The primary analysis set for the efficacy endpoints will be the mITT Population.

9.3.2. Primary Endpoints

The primary endpoints for the Safety Run-in and Part 2 Neuroblastoma Cohort Expansion are defined in Section 3; the primary endpoint for the Part 2 Neuroblastoma Cohort Expansion is also defined in Section 8.1.1.

For the Safety Run-in, the incidence of DLTs and incidence of Grade ≥3 thrombocytopenia AEs will be summarised in the DLT-evaluable Population.

For the Part 2 Neuroblastoma Cohort Expansion, the number and proportion of participants with an objective response will be tabulated. ORR will be calculated, along with its estimated 2-sided 95% CI.

9.3.3. Secondary Endpoints

The secondary efficacy endpoints for the Safety Run-in and Part 2 Neuroblastoma Cohort Expansion are defined in Section 3 and, for the Part 2 Neuroblastoma Cohort Expansion, also in Section 8.1.2.

DCR will be calculated, along with its estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR will be performed using Kaplan-Meier methods, including quartile estimates and 2-sided 95% CI. PFS and its 2-sided 95% CI will be estimated using the Kaplan-Meier method.

9.3.3.1. Safety Analyses

Safety analyses of this study are described in the master protocol.

9.3.3.2. PK Analyses

PK analyses in this study are described in the master protocol.

CCI [redacted]

9.3.3.4. Immunogenicity Analysis

Immunogenicity analysis in this study is described in the master protocol.

CCI

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The regulatory and ethical considerations of the study are outlined in Appendix 1 of the master protocol.

11. APPENDICES

The following appendices in the master protocol should be referenced for the necessary guidance for this cohort.

Appendix 1	Regulatory, Ethical, and Study Considerations
Appendix 2	Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting
Appendix 3	Contraception Guidelines
Appendix 4	Not applicable to this cohort
Appendix 5	Guidelines for Assessment of Disease, Disease Progression, and Response Criteria in Participants with Neuroblastoma – Adapted from Revised International Neuroblastoma Response Criteria (INRC)
Appendix 6	List of Abbreviations and Definitions of Terms
CCI [redacted]	
Appendix 8	Liver Safety: Required Actions and Follow-up Assessments
Appendix 9	Liver Safety Drug Restart or Rechallenge Guidelines
Appendix 12	Consideration for Participants with Past HBV Infection

APPENDIX 1. PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 01 (16 October 2020)

Overall Rationale for Amendment 01

Amendment 01 revised the protocol requirement for tumour assessments to be aligned with current standard of care and provides other clarifications and editorial changes catalogued since the issuance of the prior version of the protocol. Additionally, minor changes to the time allowed for safety reporting to ensure consistency with GSK standard practices.

Summary of Changes for the Amendment

Table 2: Summary of Changes for Amendment 01

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this version.	Editorial changes to align with the Sponsor's standard protocol template and ways of working and inclusion of specific language noted during Health Authority review
Section 1.3 Schedule of Activities	Revision to footnote for vital signs assessment to include guidance for blood pressure monitoring Deletion of minimum body weight criteria for PK parameters Revision of language for collection of information for SAEs and AEs	Alignment with niraparib safety monitoring in accordance with Investigator's Brochure, and Package Insert/Summary of Product Characteristics Deletion of information inadvertently propagated throughout protocol in error Removal of discrepant information and improved clarity
Synopsis Section 1.3 Schedule of Activities Table 4 Tumour Assessment Flowchart	Revision of preferred imaging types and schedule for scans; additionally, Schedule of Activities revised to separate imaging assessments according to different timings for standard of care and type of assessments	Allowable imaging types and schedule revised to align with current standard of care
Section 4.7.1 Procedures by Visit	Revision of preferred imaging types and schedule for scans	Allowable imaging types and schedule revised to align with current standard of care

Section(s) Affected	Description of Change	Brief Rationale
Section 4.7.2 General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic	New section added	Additional guidance to sites included in light of COVID-19
Synopsis Section 5.1 Inclusion Criteria	Minimum threshold of performance status reduced to 60% in Inclusion #4 Criteria for adequate CBC collection result revised to 1 week in Inclusion #5 Minimum threshold of absolute neutrophil count reduced to ≥1,000/μL in Inclusion #5	Revision to align with standard of care Revision to align with standard of care Revised safety monitoring guidance
Section 9.2 Analysis Populations	Immunogenicity populations included	Provided for clarity as to analysis populations intended to be studied

Abbreviations: AE=adverse event; CBC=complete blood count; COVID-19=Coronavirus Disease 2019; PK=pharmacokinetic; SAE=serious adverse event.

Amendment 02 (23 November 2020)

Overall Rationale for the Amendment

Amendment 02 revises the protocol to include specific safety language noted during Health Authority review as detailed in Table 2.

Summary of Changes for the Amendment

Table 2: Summary of Changes for Amendment 02

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, Appendix 1. Protocol Amendment History (new), and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment and administrative information for prior amendment was moved to new Appendix 1. Protocol Amendment History. Editorial changes made throughout.	Editorial changes to align with the Sponsor's standard protocol template and ways of working, for conformity, clarity, flow, and typographical error correction, and for inclusion of specific language noted during Health Authority review
Section 1.1. Synopsis (Main Criteria for Inclusion)	Clarified that participants must not be eligible for local curative treatment (criterion 1)	Participants who are eligible for local curative treatment are not permitted in the study

Section(s) Affected	Description of Change	Brief Rationale
Section 5.1. Participant Inclusion Criteria		
Section 1.1. Synopsis (Main Criteria for Exclusion) Section 5.2. Participant Exclusion Criteria	Added language for exclusion in cases of pregnant or breastfeeding participants (criterion 11) Modified that a participant should not have received a live vaccine within 30 days of starting study treatment (criterion 20) (changed from 14 days) Clarified that participants with QT interval prolongation >480 ms at screening are not eligible and no waivers are allowed (criterion 22)	Participants who are pregnant or breastfeeding are excluded from the study Participants must not receive live vaccines within 30 days of starting study treatment Participants with QT interval prolongation >480 ms at screening are not eligible for the study
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities (footnote c)	Clarified that, during the long-term Follow-Up Assessment Period, follow-up might be conducted via a clinic visit or telephone contact	To accurately reflect study conduct
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities, Table 4: Tumour Assessment Flow Chart	Updated Table 3 and Table 4 to reflect editorial updates made in the master protocol	To align with the master protocol
Section 5.3. Lifestyle Considerations	Added that participants should avoid exposure to ultraviolet light and take precautions when exposed to direct sunlight	Added due to the fact that photosensitivity has been reported for patients receiving niraparib

Amendment 03 (20 Jul 2022)

Overall Rationale for Amendment 03:

- To update secondary objective and/or endpoint for PK and immunogenicity.
- To update inclusion and exclusion criteria.
- To increase clarity and/or remove discrepancies.

All changes are listed in table below.

Table 2: Summary of Changes for Amendment 03

Section(s) Affected	Description of Change	Brief Rationale
Headers, title page, Protocol Amendment Summary of Changes, Appendix 1. Protocol Amendment History, and throughout	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment and administrative information for prior amendment was moved to Appendix 1. Protocol Amendment History. Editorial changes made throughout.	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Title page	Updated compound number "GSK4057190 to GSK4057190A"	To present current correct compound number
Section 1.1 Synopsis (Secondary objectives) Section 3 Study Objectives and Endpoints	Added new secondary objective; to assess the immunogenicity of dostarlimab in paediatric participants	To correct lack of secondary objective given immunogenicity analyses are described in the protocol and an immunogenicity population is defined in Section 9 Statistical Considerations
CCI [redacted]		
Section 1.1 Synopsis: (Methodology) Data Review Committee	Updated information for establishment and composition of an independent data oversight committee	To clarify that a committee that is independent of all aspects of the study and that is dedicated to oversight of safety and efficacy data from participants in Part 2 will be established. To clarify that details of committee composition and function will be described in a formal charter.

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		To indicate that the RP2D CCI [redacted] as determined in Part 1A of the study is the dose that is to be advanced and evaluated in Part 2 of the study.
CCI [redacted]		
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 2) Section 5.1. Participant Inclusion Criterion (criterion 2)	Deleted: Measurable disease in participants with central nervous system (CNS) involvement is defined as a tumour that is measurable in 2 perpendicular diameters on MRI and visible on more than 1 slice. Added text for measurable/evaluable disease and for bone only neuroblastoma.	To remove text that was not directly applicable to measurement of disease in neuroblastoma To further clarify exactly what type of disease would be considered measurable/evaluable.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Inclusion: criterion 6) Section 5.1. Participant Inclusion Criterion (criterion 6)	Updated note describing timing for collection of blood sample for complete blood count	To better describe a correct and more reasonable washout period for support agents (transfusion, colony-stimulating factors, erythropoietin) received prior to collection of blood for complete blood count during screening.
CCI [redacted]		
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 10) Section 5.2. Participant Exclusion Criteria (criterion 10)	Removed bullets on blood transfusion and growth factors in exclusion criterion 10	Permitted window prior to first dose of study treatment has been updated in inclusion criterion 5. The permitted windows in exclusion criterion 10 no longer are applicable and, therefore, were removed.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 15)	Deleted original exclusion criterion 15 (this text was combined with text for exclusion criterion 19 as	To update exclusion criteria to include additional criterion to support participant safety.

Section(s) Affected	Description of Change	Brief Rationale
Section 5.2. Participant Exclusion Criteria (criterion 15)	described below) and replaced with "Participant must not have a gastrointestinal condition, such as bowel obstruction, that can impact absorption of oral medications and is identified by clinical symptoms or CT scan, etc"	
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 16) Section 5.2. Participant Exclusion Criteria (criterion 16)	Updated exclusion criteria 16 to clarify guidance on hematologic side effects from prior anticancer therapy.	To clarify information on excluded cytopenia occurrence and duration
Section 1.1. Synopsis (Main Criteria for Exclusion: criterion 18) Section 5.2: Participant Exclusion Criteria (criterion 18)	Added new exclusion criteria "Toxicity related to prior immunotherapy that led to study treatment discontinuation."	To include guidance for enrolment of patients who had previously experienced toxicity in response to immunotherapy and to align eligibility requirements with those of dostarlimab protocols in general.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 19) Section 5.2. Participant Exclusion Criteria (criterion 15) Section 5.2. Participant Exclusion Criteria (criterion 19)	Deleted original exclusion criterion 15. Updated exclusion criterion 19 to clarify permitted window relative to first dose of study treatment for prior systemic anticancer therapy. Combined text from exclusion criterion 15 with text in exclusion criterion 19.	To update permitted window for receipt of prior anticancer therapy from "within 3 weeks" prior to first dose of study treatment to "within 3 weeks or 5 half-lives, whichever is shorter" - a change which was made in response to an investigator suggestion and which reflects half-life data for most common standard of care therapies enrolled patients with the specified tumour types. In addition, to make the excluded window consistent for investigational agents or devices and for approved systemic therapies of all types.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 23) Section 5.2. Participant Exclusion Criteria (criterion 23)	Updated exclusion criterion 23 with corrected QTc values	To align excluded QTc values with values appropriate for participants to be treated with dostarlimab.
Section 1.1. Synopsis (Diagnosis and Main Criteria for Exclusion: criterion 24)	Added exclusion criteria 24 to clarify that solid organ transplant is not permitted.	To prohibit enrolment of participants who are receiving immunosuppressive therapy that

Section(s) Affected	Description of Change	Brief Rationale
Section 5.2. Participant Exclusion Criteria (criterion 24)		might impact effectiveness of dostarlimab as a PD-1 inhibitor.
Section 1.1. Synopsis (Analysis Population) Section 9.2 Analysis Population Table 7	Revised definition of PK population and immunogenicity populations Updated the description of the intent-to-treat population and modified intent-to-treat population	To more accurately describe which participants qualified for inclusion in each population To more completely describe the relevant population for participants with neuroblastoma
Section 1.3. Schedule of Activities (Table 3)	Added "Post-Treatment" to column header for FUP assessment Period	To align column header content with text clarifying that Follow-up visits were to occur every 90 days following end of study treatment.
Section 1.3 Schedule of Activities (Table 3)	Removed -10-day window from Screening period	To correct outside limit of Screening activities window to -28 days rather than -28 days +10 additional days.
Section 1.3. Schedule of Activities (Table 3 and Footnote j)	Addition of pregnancy testing for WOCBP at End of Treatment and 30-day Safety Follow-up Visits	To ensure pregnancy did not occur during the excluded period.
Section 1.3. Schedule of Activities (Table 3 and Footnote l)	Addition of 12-lead ECG testing added in Cycle 3	In line with study level requirements
Section 1.3 Schedule of Activities (Table 3 and Footnote q, r)	Added text indicating that tumour assessments should be conducted every 9 weeks (every 63 [±7] days) from the start of study treatment for the first 12 months and then every 12 weeks (every 84 [±7] days) thereafter,	To reduce total number of scans conducted throughout duration of participant enrolment and thereby reduce radiation exposure overall.
Section 1.3 Table 3 Schedule of Activities	Merged cells for EOT Visit, Safety FUP Visit, and FUP Assessment Period for the rows for several disease assessment activities	To clarify that measures of disease assessment are to continue throughout the EOT and follow-up periods.
Section 1.3. Schedule of Activities (Table 3 Footnote b)	Added additional details on safety FUP visit	To clarify the Safety FUP visit window
Section 1.3. Schedule of Activities (Table 3 Footnote c)	Clarified long-term follow-up assessment period 90 (±14) days "after the last dose of study treatment"	To clearly define specific starting point from which to initiate long-term follow-up safety assessments
Section 1.3. Schedule of Activities (Table 3 Footnote i)	Updated to replace baseline with "Cycle 1 Day 1" and to clarify	To clarify that if the screening laboratory samples were

Section(s) Affected	Description of Change	Brief Rationale
	guidance for Cycle 1 Day 1 sample collection.	collected within 7 days prior to Cycle 1 Day 1, then collection of these samples did not need to be repeated for Cycle 1 Day 1.
Section 1.3 Schedule of Activities (Table 3 Footnote m)	Removed the language that "MRI should only be used if clinically appropriate, when CT is contraindicated, and preferably for imaging of the brain"	To remove restrictions to use of MRI in medically appropriate scanning situations
Section 1.3 Schedule of Activities (Table 3 Footnote v)	Added text clarifying required duration of AE collection	To clarify that collection of AEs is to continue throughout the required 30-day interval even in the event of initiation of additional anticancer treatment.
Section 1.3 Schedule of Activities (Table 3 Footnote y)	Added text clarifying collection interval for PK sample collection	To clarify that timing of PK sample collection is relative to time of participant's very first dose of niraparib.
Section 1.3. Schedule of Activities (Table 3 Footnote w, x and z)	Updated information for dostarlimab PK, ADA, neutralising antibodies, and biomarker sample collection	To provide additional guidance for procedures and timing of dostarlimab PK, ADA, and biomarker sampling.
Section 2.4 Benefits and Risks Assessment	Added new section and referred to master protocol	To align content of protocol with that of GSK standard template
Section 3 Study Objectives and Endpoints	Revised PK endpoint	To describe the parameters constituting the endpoint measures.
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Added "non-randomized"	To clarify study design.
Section 6.4. Study Treatment Compliance	Added "dostarlimab and niraparib during dostarlimab infusion visits".	To clarify exactly what study treatment would be administered to the participant at the research site and when this treatment would be administered.
Section 6.5 Dose Modification	Added clarifying text	To clarify that guidance in first paragraph of Section 6.5 is applicable to dostarlimab. To include reference to Section 4.7 in the master protocol for full dose modification guidance.
Section 6.8 Treatment Compliance	Deleted this Section	To remove text that had already been presented in the protocol in Section 6.4.

Section(s) Affected	Description of Change	Brief Rationale
Section 7.1.2 QTc Stopping Criteria	Added new section on QTc stopping criteria referring to master protocol	To align with safety monitoring requirements for dostarlimab
Section 8.1.2 Secondary Efficacy Endpoint	Added text for scan data collection	To establish that while scan data are not routinely collected in the study, these data may be collected under special circumstances.
Section 8.4 Pharmacokinetics, Immunogenicity and Biomarkers	• Added text from Master protocol Section 8.4 on PK sampling.	To provide additional detail in this supplement protocol on PK sampling requirements.
CCI [redacted]		
Section 9.3.3 Secondary Endpoints, Section 9.3.4 Interim Analysis, and Section 9.3.5 Exploratory Analysis	Reordered sections / subsections	Reordered sections/ subsections to more clearly present planned analyses.
Section 11 Appendices	Updated Appendix numbers and added new Appendix 5 Guidelines for Assessment of Disease, Disease Progression, and Response Criteria in Participants with Neuroblastoma – Adapted from Revised International Neuroblastoma Response Criteria (INRC) and cross refereed to master protocol	To direct the reader to the appropriate guidance in the master protocol for assessing response in participants with neuroblastoma.

Amendment 04 (23 May 2024)

Overall Rationale for Amendment 04:

Amendment 04 is a global amendment resulting in changes in participant dosing based on the participant's age. Administrative, editorial, and clarifications for study conduct are also included. A general description and brief rationale(s) for the key changes are provided in Table 2 below. The synopsis was also updated to align with the changes in the protocol body.

Table 2: Summary of Changes for Amendment 04

Section(s) Affected	Description of Change	Brief Rationale
Headers, Title Page, abbreviations, Protocol Amendment Summary of Changes, List of Abbreviations, Appendices, References, and throughout Section 6 Study Treatment(s) and Concomitant Therapy	Headers and title page updated with new document numbers, dates, and amendment information; Protocol Amendment Summary of Changes section was updated to include details and rationales for this amendment; administrative changes, editorial revisions for consistency with Sponsor's ways of working, minor corrections and formatting adjustments, and to add clarification and/or remove discrepancies	Editorial changes to align with the Sponsor's standard protocol template, style guide, and ways of working and regulatory changes, and for accuracy, clarity, conformity, flow, and typographical error correction.
Throughout	• Use of CCI changed to CCI throughout the document, including CCI details and use of CCI going forward, as applicable	CCI is the selected CCI [redacted] developed by the applicant for use in participants and is a term commonly used by the Sponsor's formulation development and manufacturing groups
Section 1.3 Schedule of Assessments (Table 3, footnotes) Section 1.2 Schemas, Figure 1 (new) Section 2 Introduction Section 3, Table 5 Objectives and Endpoints for Study 213406 Section 4.1 Overall Design Section 4.1.1 Dose Limiting Toxicity Section 4.2 Number of Participants Section 4.4 Dose Adjustment Criteria Section 4.4.1 Dose Adjustment Criteria for Age and Weight Section 4.4.2 Dose Adjustment for AEs Section 4.4.3 Niraparib Section 4.4.4 dostarlimab Section 5.1 Participant Inclusion Criterion Section 6.1 Study Treatments Administered; Table 9: Investigational Products Section 8.1 Assessment of Efficacy Section 9.1 Sample Size Determination Section 9.2 Analysis Populations Section 9.3.2 Primary Endpoints Section 9.3.3 Secondary Endpoints	• New figure outlining Part 2 study design • Footnotes updated in SoA regarding monitoring/PK sample collection with changes in niraparib dose during the study per the updated dosing regimens based on weight and age • Introduction and study objectives and endpoints updated to include the Safety Run-in Cohort participants • Update overall design to reflect updated dosing and details of Safety Run-in • Section 4.4.1 and Section 4.4.2 added outlining dose adjustments for age and weight and AEs in Part 2 • Section 4.4.3 included for guidance on niraparib dose reductions and Table 6, Table 7, and Table 8 added outlining modifications for AEs, nonhematologic adverse reactions, and haematologic adverse reactions, respectively • Subsection included referring to dostarlimab dose modification • Inclusion criterion #3 – updated to outline age enrolment requirements under Amendment 04 • Inclusion criterion #4 – updated to reflect no requirement for ability to swallow as a result of CCI formulation being used going forward	Changes to proposed dosing regimens for niraparib and study design, following study enrolment pause and data evaluation to ensure appropriate dosing of participants with the combination, including additional cohorts to evaluate additional dose levels Minor editorial changes to endpoints and objectives for clarification.

Section(s) Affected	Description of Change	Brief Rationale
	• Number of participants updated to include Safety Run-in Cohort patients • Study treatment information sections update to include CCI details • Including update to Investigation products table to align with regulatory requirements • Sample size text updated to reflect addition of Safety Run-in • Updated assessment of efficacy section and statistical analyses sections to include Safety Run-in information, definition for DTL-evaluable Population	
Section 3, Table 5 Objectives and Endpoints for Study 213406 9.3.5 Exploratory Analysis	• Exploratory endpoints updated to adjust wording for exploratory biomarker objective and endpoint language as well as exploratory analysis	To provide further details and more clarity about the planned exploratory analysis.
Section 5.1 Participant Inclusion Criteria	• Inclusion criterion #6: organ function parameters updated for haemoglobin	To align with the patient population
Section 1.3 Schedule of Assessments (Table 3, footnote) Section 5.1 Participant Inclusion Criteria (criterion #7c)	• Clarification included that WOCBP must have a pregnancy test even if they had received treatment that potentially but not definitely would prohibit becoming pregnant • Timeline for providing negative pregnancy test result updated to 24 hours	Updated to increase assurance that female participant of childbearing potential is not pregnant as close as possible to time of study drug dosing
Section 5.2 Participant Exclusion Criteria	• Exclusion criterion #7 – clarification participants with previously treated CNS metastases for evidence of disease progression	Updated text to provide more accurate description of changes indicative of progression of disease in brain.
Section 5.2 Participant Exclusion Criteria	• Exclusion criterion #11 – updated language regarding when breastfeeding can resume	To align with guidance in current US prescribing information for niraparib and dostarlimab
Section 5.2. Participant Exclusion Criteria	• Exclusion criterion 14 – updated wording regarding HbsAg/HbcAb for HBV screening	To permit the inclusion of patients with past HBV infection
Section 5.2. Participant Exclusion Criteria	• New exclusion criteria #25 and #26 added regarding HCV testing	To align with current protocol template language
Section 5.2. Participant Exclusion Criteria	• Exclusion criterion #17 – updated language regarding AEs in participants undergoing systemic anticancer therapy with exceptions as agreed with Sponsor.	Expansion of text to more clearly define conditions for participant eligibility.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Schedule of Assessments (Table 3)	CCI [redacted]	
Section 2.2 Rationale for Tumour Type	• CCI [redacted]	Editorial change for clarification
Section 5.1. Participant Inclusion Criteria	• Inclusion criterion #1 – replaced statement '***local curative treatment***.' with '***alternative curative treatment***.'	Clarification
Section 5.1 Participant Inclusion criteria	• Inclusion criterion #10 – updated clarifying tumour tissue sample requirements	Clarification
Section 1.3. Schedule of Activities (Table 3, including footnotes) Section 4.4 General Study Conduct Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	• Update to blood sample collection for niraparib PK • Adjusted table and added clarifying footnote for blood sampling for dostarlimab PK and/or ADAs and neutralising antibodies (NAb) at Safety FUP Visit and FUP Assessment Period • Updated language regarding collection of blood samples and storage	Clarification for study conduct and alignment with Sponsor requirements for sample storage
Section 1.3 Schedule of Assessments (Table 3 and Table 4; including footnotes) Table 4 Tumour Assessment Flowchart	• Clarification that brain scans must include IV contrast and brain scan by MRI preferred to that by CT including in table footnote and Table 4 outlining tumour assessments • Wording and footnote updates in SoA for clarifications including aligning discontinuation wording throughout.	Clarification for study conduct
Section 1.3 Schedule of Assessments (Table 3; footnote) Section 8.2 Assessment of Safety Section 8.4 Pharmacokinetics, Immunogenicity, and Biomarkers	• Detail included regarding prioritisation of blood sample collection in the event of concerns for excessive blood volume withdrawal	Clarification for study conduct to provide guidance to sites on relative importance of collection of specific blood samples
Section 1.3 Schedule of Assessments (Table 3; including footnote) 8.4.1 exploratory biomarkers	• Updated language regarding collection and analysis of biomarker samples and processing	Clarification

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (Table 3; including footnote)	• Updated timing for collection of vital signs, height, and weight measurements including during follow-up period and clarifications for measuring height and weight • CCI [redacted] • Adjusted wording surrounding collection and follow-up of nonserious AEs, and expectations for follow-up of SAEs during long-term follow-up period and when starting alternative anticancer therapy	Clarification for study conduct, including adjusted language to permit consistent monitoring of vital signs throughout the Treatment Period.
Section 8.5 Genetics	• Updated language outlining DNA analysis	Clarification

Abbreviations: CCI [redacted]; ADA(s)=antidrug antibody(ies); AE(s)=adverse event(s); CCI [redacted]; CBC=complete blood count; CNS=central nervous system; CT=computed tomography; DLT=dose limiting toxicity(ies); FUP=follow-up; GFR=glomerular filtration rate; HbcAb=hepatitis B core antibody, HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV=hepatitis C virus; INRC=International Neuroblastoma Response Criteria; MRI=magnetic resonance imaging; MIBG-SPECT=metaiodobenzylguanidine-single photon emission computed tomography/computed tomography; PK=pharmacokinetics; RECIST=Response Evaluation Criteria in Solid Tumours; SAE(s)=serious AE(s); SoA=schedule of assessments; CCI [redacted]; WOCBP=woman of childbearing potential; US=United States.

Amendment 04 GBR-1(08 Aug 2024)
Overall Rationale for Amendment 04 GBR-1:
Amendment 04 GBR-1 is a UK-specific amendment addressing agency feedback regarding exclusion criterion 17. A description and rationale for the changes is provided in Table 2 below.

Table 2: Summary of Changes for Amendment 04 GBR-1

Section(s) Affected	Description of Change (~~deleted text~~; **added text**)	Brief Rationale
Headers, Title Page, Protocol Amendment Summary of Changes, Appendix 2 Country-specific Requirements	Headers and title page updated with new amendment number/approval date, and amendment information; Protocol Amendment Summary of Changes section was updated to include details and rationale for this amendment; country-specific appendix for global amendments removed and associated text in protocol sections/tables adjusted.	Editorial changes to align with the Sponsor's standard protocol template, style guide, and ways of working.

Section(s) Affected	Description of Change (~~deleted text~~; **added text**)	Brief Rationale
Synopsis Section 5.2 Participant Exclusion Criteria	Exclusion criterion #17 updated as follows: Participant has not recovered (i.e., to Grade ≤1 or to baseline) from systemic **anticance**r therapy-induced AEs. Note: Participants with ~~certain AEs that are considered either nonclinically significant or are deemed stable or irreversible are exceptions to this criterion and may qualify for the study after discussion with the GSK Medical Monitor. Examples of AEs include, but are not limited to, alopecia,~~ hearing impairment, **alopecia**, Grade ≤2 neuropathy, Grade ≤2 fatigue, Grade ≤2 anaemia, and/**or** Grade ≤2 neutropenia **are an exception to this criterion and may qualify for the study.**	Regulatory agency feedback.

CCI

[redacted]

12. LIST OF REFERENCES

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