Clinical trial results:
A Phase I, Open-label, Parallel Group Study to Investigate Olaparib Safety and Tolerability, Efficacy and Pharmacokinetics in Paediatric Patients with Solid Tumours

Summary

EudraCT number	2018-003355-38
Trial protocol	GB DE ES DK HU IT AT PL
Global end of trial date	04 February 2025

Results information

Result version number	v1 (current)
This version publication date	20 August 2025
First version publication date	20 August 2025

Trial information

Trial identification

Sponsor protocol code	D0816C00025

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04236414
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002269-PIP01-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2025
Global end of trial reached?	Yes
Global end of trial date	04 February 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To describe the safety and tolerability of olaparib monotherapy and identify the recommended phase II dose (RP2D) of olaparib in the paediatric population.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	16
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	3
Adolescents (12-17 years)	13
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study had 2 phases: dose-finding and signal identification.
Dose-finding included those with homologous recombination repair (HRR) deficiency per local test.
Signal identification included those with deleterious/suspected HRR gene mutations or by central germline breast cancer susceptibility gene (BRCA) test and needed to receive the RP2D.

Pre-assignment

Screening details:

Dose-finding phase included 13 participants (Cohort A: 10 participants aged ≥12 to <18; Cohort B: 3 participants aged ≥3 to <12). Signal identification phase included 5 participants, 3 from the dose-finding phase (2 from Cohort A, 1 from Cohort B).
1 additional participant was not evaluable but was counted in the overall total.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Cohort A (Dose Finding phase)

Arm description:

Participants with HRR deficiency aged ≥12 to <18 years

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Up to 300 mg received as a single dose on Day 1, followed by initiation of twice daily continuous dosing from Day 2 onwards taken at the same time each day (morning and evening), approximately 12 hours apart.

Arm title	Cohort B (Dose-finding phase)

Arm description:

Participants with HRR deficiency aged ≥3 to <12 years

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Up to 200 mg received as a single dose on Day 1, followed by initiation of twice daily continuous dosing from Day 2 onwards taken at the same time each day (morning and evening), approximately 12 hours apart.

Arm title	Signal identification phase

Arm description:

Participants with a confirmed HRR gene mutation, including participants from the dose-finding phase, and needed to receive the RP2D

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg (for participants aged 6-11) and 300 mg (for participants aged 12-17) received as a single dose on Day 1, followed by initiation of twice daily continuous dosing from Day 2 onwards taken at the same time each day (morning and evening), approximately 12 hours apart.

Arm title	Overall Total

Arm description:

Participants in the dose-finding and signal identification phases, including any patients who entered the signal identification phase but were not evaluable for analysis (ie, did not have an HRR gene mutation confirmed via central testing)

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Refer to dosage and administration details provided for Cohorts A, B, and Signal Identification Phase.

Number of subjects in period 1	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase
Started	10	3	5
Completed	0	0	0
Not completed	10	3	5
Death [Incl pts who die in surv fwup]	8	-	2
Consent withdrawn by subject	-	2	2
Other	2	-	1
Lost to follow-up	-	1	-

Number of subjects in period 1	Overall Total
Started	16
Completed	0
Not completed	16
Death [Incl pts who die in surv fwup]	8
Consent withdrawn by subject	4
Other	3
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (Dose Finding phase)
Reporting group description:	
Participants with HRR deficiency aged ≥12 to <18 years	
Reporting group title	Cohort B (Dose-finding phase)
Reporting group description:	
Participants with HRR deficiency aged ≥3 to <12 years	
Reporting group title	Signal identification phase
Reporting group description:	
Participants with a confirmed HRR gene mutation, including participants from the dose-finding phase, and needed to receive the RP2D	
Reporting group title	Overall Total
Reporting group description:	
Participants in the dose-finding and signal identification phases, including any patients who entered the signal identification phase but were not evaluable for analysis (ie, did not have an HRR gene mutation confirmed via central testing)	

Reporting group values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase
Number of subjects	10	3	5
Age categorical			
The overall total number of participants was 16 instead of 18.			
Units: Subjects			
Participants aged ≥12 to <18 years	10	0	4
Participants aged ≥3 to <12 years	0	3	1
Age Continuous			
Age at Screening			
Units: Years			
arithmetic mean	15.1	8.3	13.0
standard deviation	± 2.13	± 2.52	± 4.24
Sex: Female, Male			
The overall total number of participants was 16 instead of 18. The 2 female participants from the signal identification arm were also in Cohort A.			
Units: Participants			
Female	3	0	2
Male	7	3	3
Race/Ethnicity, Customized			
The overall total number of participants was 16 instead of 18. The 2 "Other" participants from the signal identification arm were also in Cohort A.			
Units: Subjects			
Asian	4	2	2
White	4	1	1
Other	2	0	2
Race/Ethnicity, Customized			
The overall total number of participants was 16 instead of 18. The 2 participants from the signal identification arm were also in Cohort A and 1 participant was also in Cohort B.			
Units: Subjects			
Not Hispanic or Latino	10	3	5

Reporting group values	Overall Total	Total	
Number of subjects	16	34	
Age categorical			
The overall total number of participants was 16 instead of 18.			
Units: Subjects			
Participants aged ≥12 to <18 years	13	27	
Participants aged ≥3 to <12 years	3	7	
Age Continuous			
Age at Screening			
Units: Years			
arithmetic mean	14.0		
standard deviation	± 3.43	-	
Sex: Female, Male			
The overall total number of participants was 16 instead of 18. The 2 female participants from the signal identification arm were also in Cohort A.			
Units: Participants			
Female	3	8	
Male	13	26	
Race/Ethnicity, Customized			
The overall total number of participants was 16 instead of 18. The 2 "Other" participants from the signal identification arm were also in Cohort A.			
Units: Subjects			
Asian	8	16	
White	6	12	
Other	2	6	
Race/Ethnicity, Customized			
The overall total number of participants was 16 instead of 18. The 2 participants from the signal identification arm were also in Cohort A and 1 participant was also in Cohort B.			
Units: Subjects			
Not Hispanic or Latino	16	32	

End points

End points reporting groups

Reporting group title	Cohort A (Dose Finding phase)
Reporting group description: Participants with HRR deficiency aged ≥12 to <18 years	
Reporting group title	Cohort B (Dose-finding phase)
Reporting group description: Participants with HRR deficiency aged ≥3 to <12 years	
Reporting group title	Signal identification phase
Reporting group description: Participants with a confirmed HRR gene mutation, including participants from the dose-finding phase, and needed to receive the RP2D	
Reporting group title	Overall Total
Reporting group description: Participants in the dose-finding and signal identification phases, including any patients who entered the signal identification phase but were not evaluable for analysis (ie, did not have an HRR gene mutation confirmed via central testing)	

Primary: Dose-limiting toxicity (DLT) events

End point title	Dose-limiting toxicity (DLT) events[1][2]
End point description: To describe the safety and tolerability of olaparib monotherapy. The number of participants who experienced DLTs are presented.	
End point type	Primary
End point timeframe: 1 cycle of 28 days of therapy	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Participants				
Number of evaluable participants	6	3		
Number of evaluable participants with a DLT	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Discontinuation rate of olaparib treatment due to AEs throughout the study

End point title	Discontinuation rate of olaparib treatment due to AEs throughout the study[3]

End point description:

To describe the safety and tolerability of olaparib monotherapy.
The number of participants who discontinued olaparib treatment due to AEs is presented.

End point type	Primary

End point timeframe:

Time of signature of ICF throughout the treatment period and including the 30-day follow-up period.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	Overall Total
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	3	5	16
Units: Participants	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: Cmax

End point title	Pharmacokinetic parameter: Cmax[4]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg twice daily (bd) tablet) dose based upon PK modelling.
The median plasma concentration of olaparib on Day 1 is presented. No plasma samples were collected for participants in Cohort A on Day 1.
Cmax = maximum concentration

End point type	Secondary

End point timeframe:

Day 1

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort B (Dose-finding phase)	Signal identification phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: ug/mL				
median (full range (min-max))	8.989 (7.45 to 9.01)	7.201 (0.825 to 9.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: Css,max

End point title	Pharmacokinetic parameter: Css,max[5]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
Plasma steady state PK was achieved on Day 8, based on visual comparison of Day 1 and Day 8 trough concentrations. The median plasma concentration of olaparib on Day 8 is presented.
Css,max = maximum plasma concentration at steady state

End point type	Secondary

End point timeframe:

Day 8

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: ug/mL				
median (full range (min-max))	7.293 (2.47 to 19.6)	10.42 (6.99 to 10.9)	10.42 (0.680 to 13.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: CLss/F

End point title	Pharmacokinetic parameter: CLss/F[6]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
Plasma steady state PK was achieved on Day 8, based on visual comparison of Day 1 and Day 8 trough concentrations. The median plasma concentration of olaparib on Day 8 is presented.
CLss/F = apparent total clearance of the drug from plasma at steady state after oral administration

End point type	Secondary

End point timeframe:

Day 8

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: L/h				
median (full range (min-max))	6.866 (1.96 to 11.2)	4.634 (4.34 to 5.78)	5.784 (3.01 to 105)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: tmax

End point title	Pharmacokinetic parameter: tmax[7]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
The median plasma concentration of olaparib on Day 1 is presented. No plasma samples were collected for participants in Cohort A on Day 1.
tmax = time to maximum concentration

End point type	Secondary

End point timeframe:

Day 1

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort B (Dose-finding phase)	Signal identification phase		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	5		
Units: hours (h)				
median (full range (min-max))	1.03 (1.00 to 1.95)	1.95 (1.03 to 2.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: Css,min

End point title	Pharmacokinetic parameter: Css,min[8]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
Plasma steady state PK was achieved on Day 8, based on visual comparison of Day 1 and Day 8 trough concentrations. The median plasma concentration of olaparib on Day 8 is presented.
Css,min = minimum plasma concentration at steady state

End point type	Secondary

End point timeframe:

Day 8

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: ug/mL				
median (full range (min-max))	1.810 (0.828 to 8.22)	0.6177 (0.381 to 1.37)	1.710 (0.0277 to 6.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: Css,max/D

End point title	Pharmacokinetic parameter: Css,max/D[9]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
Plasma steady state PK was achieved on Day 8, based on visual comparison of Day 1 and Day 8 trough

concentrations. The median plasma concentration of olaparib on Day 8 is presented.
Css,max/D = dose normalised maximum plasma concentration at steady state

End point type	Secondary

End point timeframe:

Day 8

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: ug/mL/mg				
median (full range (min-max))	0.02431 (0.00823 to 0.0654)	0.05212 (0.0350 to 0.0545)	0.03599 (0.00227 to 0.0521)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: tss,max

End point title	Pharmacokinetic parameter: tss,max[10]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
Plasma steady state PK was achieved on Day 8, based on visual comparison of Day 1 and Day 8 trough concentrations. The median plasma concentration of olaparib on Day 8 is presented.
tss,max = time to maximum plasma concentration at steady state

End point type	Secondary

End point timeframe:

Day 8

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: hours (h)				
median (full range (min-max))	1.52 (1.50 to	1.98 (1.93 to	1.93 (1.50 to	

6.03)	2.00)	4.02)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: AUCss

End point title	Pharmacokinetic parameter: AUCss[11]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
The median AUCss on Day 8 is presented.
AUCss = area under the curve at steady state

End point type	Secondary

End point timeframe:

Day 8

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: h*ug/mL				
median (full range (min-max))	45.71 (26.9 to 153)	43.16 (34.6 to 46.1)	36.11 (2.86 to 99.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: AUC (0-8)

End point title	Pharmacokinetic parameter: AUC (0-8)[12]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
The median AUC (0-8) on Day 1 and Day 8 is presented. No plasma samples were collected for participants in Cohort A on Day 1.
AUC (0-8) = area under the curve at 0-8 hours

End point type	Secondary

End point timeframe:

Day 1 to Day 8

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: h*ug/mL				
median (full range (min-max))				
Day 1	0 (0 to 0)	27.61 (27.5 to 30.0)	27.54 (2.00 to 42.6)	
Day 8	37.17 (18.3 to 114)	37.55 (32.1 to 42.6)	32.08 (2.67 to 71.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: AUCss/D

End point title	Pharmacokinetic parameter: AUCss/D[13]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
The median AUCss/D on Day 8 is presented.
AUCss/D = dose normalised area under the curve at steady state

End point type	Secondary

End point timeframe:

Day 8

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: h*ug/mL/mg				
median (full range (min-max))	0.1524 (0.0897 to	0.2158 (0.173 to 0.230)	0.1729 (0.00954 to	

0.511)	0.332)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic parameter: AUC (0-t)

End point title	Pharmacokinetic parameter: AUC (0-t)[14]

End point description:

To describe the paediatric PK profile and to identify the adult equivalent (300 mg bd tablet) dose based upon PK modelling.
The median AUC (0-t) on Day 1 and Day 8 is presented. No plasma samples were collected for participants in Cohort A on Day 1.
AUC (0-t) = area under the curve from zero up to time t

End point type	Secondary

End point timeframe:

Day 1 to Day 8

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: There was no formal statistical analysis of safety and tolerability data or efficacy data in this study. Demographic and other baseline disease characteristics, concomitant medication, dosing, exposure, safety, tolerability, dose limiting toxicities, efficacy data, and protocol deviations were listed and summarised by cohort and overall in the dose-finding phase, overall in the signal identification phase and in the total study, as appropriate.

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	5	
Units: h*ug/mL				
median (full range (min-max))				
Day 1	0 (0 to 0)	29.53 (28.9 to 32.5)	29.53 (2.40 to 73.7)	
Day 8	45.71 (26.9 to 153)	43.16 (34.6 to 46.1)	36.11 (2.86 to 99.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: DCR as defined by Investigator-assessed RECIST v.1.1, INRC, or RANO

End point title	DCR as defined by Investigator-assessed RECIST v.1.1, INRC, or RANO

End point description:

Disease control rate (DCR) was defined as the percentage of participants who have a best objective response (BOR) of CR, PR, minor response (MR) (if applicable) or who have stable disease (without subsequent cancer therapy) for at least 7 weeks after start of treatment (to allow for an early

assessment within the assessment window) in participants with measurable disease.

End point type	Secondary

End point timeframe:

Every 8 weeks (±1 week) relative to the date of treatment initiation until week 24, and every 12 weeks (±1 week) thereafter until objective disease progression or withdrawal

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	Overall Total
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	3	12
Units: Percentage	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: ORR as defined by Investigator-assessed RECIST v.1.1, INRC, or RANO

End point title	ORR as defined by Investigator-assessed RECIST v.1.1, INRC, or RANO

End point description:

Objective response rate (ORR) was defined as the percentage of patients with an investigator-assessed response of complete response (CR) or partial response (PR) as per RECIST v1.1, INRC or RANO and was based on a subset of all treated patients with measurable disease at baseline per the site investigator. INRC = International Neuroblastoma Response Criteria RECIST = Response Evaluation Criteria in Solid tumours RANO = Response Assessment in Neuro-oncology

End point type	Secondary

End point timeframe:

Every 8 weeks (±1 week) relative to the date of treatment initiation until week 24, and every 12 weeks (±1 week) thereafter until objective disease progression or withdrawal

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	Overall Total
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	5	12
Units: Percentage				
number (confidence interval 95%)	0 (0 to 40.96)	0 (0 to 70.76)	0 (0 to 70.76)	0 (0 to 26.46)

Statistical analyses

No statistical analyses for this end point

Secondary: DoR as defined by Investigator-assessed RECIST v.1.1, INRC, or RANO

End point title	DoR as defined by Investigator-assessed RECIST v.1.1, INRC, or RANO

End point description:

Duration of response (DoR) was defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The time of the initial response will be defined as the date of the first visit response that was CR or PR. No participants had an objective response (BOR of CR or PR) and hence the DoR could not be summarised.

End point type	Secondary

End point timeframe:

Every 8 weeks (±1 week) relative to the date of treatment initiation until week 24, and every 12 weeks (±1 week) thereafter until objective disease progression or withdrawal

End point values	Cohort A (Dose Finding phase)	Cohort B (Dose-finding phase)	Signal identification phase	Overall Total
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[15]	0[16]	0[17]	0[18]
Units: weeks				

Notes:

[15] - No participants had a BOR of CR or PR and hence the DoR could not be summarised.

[16] - No participants had a BOR of CR or PR and hence the DoR could not be summarised.

[17] - No participants had a BOR of CR or PR and hence the DoR could not be summarised.

[18] - No participants had a BOR of CR or PR and hence the DoR could not be summarised.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be collected from time of signature of ICF throughout the treatment period and including the 30-day follow-up period.

Adverse event reporting additional description:

Includes AEs with an onset date or that worsen on or after the first dose of study treatment up to (and including) 30 days after the last dose date or until the initiation of the first subsequent anti-cancer therapy, whichever occurs first.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Cohort A (Dose-finding phase)

Reporting group description:

Participants with HRR deficiency aged ≥12 years to <18 years

Reporting group title	Overall Total

Reporting group description:

Patients in the dose-finding and signal identification phases, including any participant who entered the signal identification phase but was not evaluable for analysis (ie, did not have a confirmed HRR gene mutation)

Reporting group title	Signal identification phase

Reporting group description:

Participants with a confirmed HRR gene mutation, including participants from the dose-finding phase

Reporting group title	Cohort B (Dose-finding phase)

Reporting group description:

Participants with HRR deficiency aged ≥3 years to <12 years

Serious adverse events	Cohort A (Dose-finding phase)	Overall Total	Signal identification phase
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	4 / 16 (25.00%)	2 / 5 (40.00%)
number of deaths (all causes)	9	9	2
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort B (Dose-finding phase)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Optic neuropathy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort A (Dose-finding phase)	Overall Total	Signal identification phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	15 / 16 (93.75%)	5 / 5 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Hot flush			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Jugular vein thrombosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Non-cardiac chest pain			

subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	4 / 16 (25.00%)	2 / 5 (40.00%)
occurrences (all)	4	5	2
Chest discomfort			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Asthenia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	2 / 5 (40.00%)
occurrences (all)	2	2	2
Chills			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Hypoxia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Cough			
subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	1 / 5 (20.00%)
occurrences (all)	2	2	1
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	3	3
Platelet count decreased			
subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	0 / 5 (0.00%)
occurrences (all)	4	4	0
Tri-iodothyronine free decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
White blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 16 (12.50%)	1 / 5 (20.00%)
occurrences (all)	1	2	1
C-reactive protein increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 16 (12.50%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	2	2	0

Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Neuralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 16 (18.75%)	2 / 5 (40.00%)
occurrences (all)	1	4	3
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 16 (18.75%)	2 / 5 (40.00%)
occurrences (all)	1	5	4
Anaemia			
subjects affected / exposed	6 / 10 (60.00%)	9 / 16 (56.25%)	2 / 5 (40.00%)
occurrences (all)	8	12	2
Lymphopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 16 (18.75%)	2 / 5 (40.00%)
occurrences (all)	1	4	3
Eye disorders			
Optic neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Gingival bleeding			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1

Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	3 / 16 (18.75%)	2 / 5 (40.00%)
occurrences (all)	3	4	3
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Ascites			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	1 / 5 (20.00%)
occurrences (all)	3	3	1
Abdominal discomfort			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Mouth ulceration			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Vomiting			
subjects affected / exposed	6 / 10 (60.00%)	7 / 16 (43.75%)	2 / 5 (40.00%)
occurrences (all)	8	9	2
Stomatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	4 / 10 (40.00%)	5 / 16 (31.25%)	2 / 5 (40.00%)
occurrences (all)	5	6	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Haematuria			

subjects affected / exposed	2 / 10 (20.00%)	2 / 16 (12.50%)	2 / 5 (40.00%)
occurrences (all)	2	2	2
Hydronephrosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Central hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Covid-19			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypophagia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Hyponatraemia			
subjects affected / exposed	2 / 10 (20.00%)	4 / 16 (25.00%)	1 / 5 (20.00%)
occurrences (all)	2	4	1

Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)	5 / 16 (31.25%)	2 / 5 (40.00%)
occurrences (all)	3	5	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 16 (6.25%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	2 / 10 (20.00%)	3 / 16 (18.75%)	0 / 5 (0.00%)
occurrences (all)	2	3	0

Non-serious adverse events	Cohort B (Dose-finding phase)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Jugular vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		

Chest discomfort subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Asthenia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Chills subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Hypoxia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Epistaxis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dyspnoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Cough subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		

Tri-iodothyronine free decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Injury, poisoning and procedural complications Back injury subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Nervous system disorders Loss of consciousness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dizziness			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Neuralgia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Anaemia			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	3		
Lymphopenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Eye disorders			
Optic neuropathy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Constipation			

subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hydronephrosis			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Endocrine disorders			
Central hypothyroidism			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Infections and infestations			
Covid-19			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hypophagia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

Decreased appetite subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2019	Febrile neutropenia of CTCAE ≥3 is considered a standard definition for a DLT in Phase I dose-finding studies where defining safety and tolerability is a primary objective.
18 May 2020	The primary reason for this protocol amendment was to permit patients with primary CNS tumours entry into the study. In addition, revisions were made in response to questions from the Health Authorities, to align with current practice and to clarify procedures.
30 September 2021	The primary reasons for this protocol amendment were to include details for the AAF and to include saliva sampling for PK analysis. In addition, revisions were made to clarify procedures based on Health Authority feedback. Furthermore, additional study mitigation language was added to provide sites with measures that could be implemented during the COVID-19 pandemic.
21 May 2024	The primary reasons for this protocol amendment were to prepare for the transition to European Union Clinical Trial Regulation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was terminated on 29 January 2025 due to operational futility per CSP criteria (<5 participants/year with HRR mutations). Last patient last visit (LPLV) occurred on 04 February 2025; all data were analyzed using a DCO date of 28 February 2025.

Notes: