Clinical trial results:
International phase I/II expansion trial of the MEK inhibitor selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult Acute Lymphoblastic Leukaemia

Summary

EudraCT number	2016-003904-29
Trial protocol	GB NL FR DK
Global end of trial date	26 August 2021

Results information

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

Trial information

Trial identification

Sponsor protocol code	RG_16-186

Additional study identifiers

ISRCTN number	ISRCTN92323261
ClinicalTrials.gov id (NCT number)	NCT03705507
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Joshua Savage, University of Birmingham, seludex@trials.bham.ac.uk
Scientific contact	Joshua Savage, University of Birmingham, seludex@trials.bham.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2021
Global end of trial reached?	Yes
Global end of trial date	26 August 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To define the recommended phase II dose (RP2D) of selumetinib in combination with dexamethasone in adult and paediatric patients with relapsed/refractory, RAS pathway mutant ALL, and to assess the preliminary anti-leukemic activity of the combination in those patients.

Protection of trial subjects:

Trial Safety Commitee (TSC) was established to provide independent oversight of the trial and provide advice through its independent chair. The TSC will include a patient representative and a sponsor's representative. The Chief Investigator will report to the committee on behalf of the TMG. The TSC will assume responsibility for the oversight of the trial on behalf of the Coordinating Sponsor. The TSC will meet or hold teleconferences at least once a year, or more often if required. The TSC will take on the responsibilities similar to that of a data monitoring committee on late phase trials. Established by the Sponsor, the TSC will assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, including dose decisions, and to recommend to the Sponsor whether to continue, modify, or stop a trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 April 2018
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	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	12
EEA total number of subjects	2

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)	1
Adults (18-64 years)	4
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial opened to recruitment on 17th April 2018 with the first patient recruited on 18th May 2018. The last patient was recruited on 10th August 2021 and the trial closed to recruitment on 3rd May 2023. Patients were recruited from sites across the UK, and one site in the Netherlands. Sites also opened in France & Denmark but did not recruit.

Pre-assignment

Screening details:

RAS pathway activating mutations (NRAS, KRAS, FLT3, PTPN11, cCBL, NF1, BRAF, IKZF2, IKZF3, IL7Rα or JAK1) were identified during the trial screening process with local analysis or central analysis by Northern Genetics Service.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Group A enrolled patients who are 18 years or older

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

Dosage and administration details:

All patients entered onto the dose finding element of the trial will receive treatment as per protocol. Starting dose (dose level 0) 75mg BD PO. Cycle 1 D1: single dose, Cycle 1 D4-D28: BD dosing, Subsequent cycles 2-6: D1-28: BD dosing.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cycle 1 D2-4 & D8-11: 6mg/m2/day, D15-18 & D22-25: 4mg/m2/day.
Cycle 2 D1-4: 4mg/m2/day
Subsequent cycles 3-6, D1-5 only 6mg/m2/day

Arm title	Group P

Arm description:

Group P enrolled patients under 18 years of age

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

Dosage and administration details:

All patients entered onto the dose finding element of the trial will receive treatment as per protocol. Starting dose (dose level -1) 20mg/m2 BD PO. Cycle 1 D1 single dose, Cycle 1 D4-D28: BD dosing, Subsequent cycles 2-6: D1-28: BD dosing.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cycle 1 D2-4 & D8-11: 6mg/m2/day, D15-18 & D22-25: 4mg/m2/day.
Cycle 2 D1-4: 4mg/m2/day
Subsequent cycles 3-6, D1-5 only 6mg/m2/day

Number of subjects in period 1	Group A	Group P
Started	8	4
Completed	7	4
Not completed	1	0
Died before starting trial treatment	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	3	3	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	4	4	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
median	25		
full range (min-max)	5 to 73	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	10	10	
Ethnicity Units: Subjects			
Any other Asian background	1	1	
Any other ethnic group	1	1	
Arab	1	1	
Bangladeshi	1	1	
Caribbean	1	1	
English/Welsh/Scottish/Northern Irish/British	7	7	
Current ALL disease status Units: Subjects			
Progressive	1	1	
Refractory	2	2	
Relapsed	9	9	
CNS disease status at diagnosis Units: Subjects			
CNS1	7	7	
CNS2	1	1	
CNS3	1	1	
Unknown	3	3	
Previously received CAR T cell therapy			

Units: Subjects			
No	9	9	
Yes	3	3	
Previously received HSCT Units: Subjects			
No	7	7	
Yes	5	5	
ALL classification Units: Subjects			
B-cell precursor ALL	6	6	
T-ALL	6	6	
ECOG Performance Status Units: Subjects			
PS0	1	1	
PS1	4	4	
PS2	1	1	
Unknown	6	6	
Bone marrow blast score Units: Subjects			
M2	2	2	
M3	9	9	
Unknown	1	1	
Cellularity Units: Subjects			
Hypercellular	5	5	
Hypocellular	2	2	
Normocellular	3	3	
Unknown	2	2	
CNS disease classification in CSF Units: Subjects			
CNS1	10	10	
CNS3	1	1	
Unknown	1	1	
Weight Units: kilogram(s)			
median	67		
full range (min-max)	27 to 128	-	
Height Units: metre			
median	1.71		
full range (min-max)	1.17 to 1.89	-	
Body Surface Area Units: m2			
median	1.79		
full range (min-max)	0.96 to 2.60	-	

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
Group A enrolled patients who are 18 years or older	
Reporting group title	Group P
Reporting group description:	
Group P enrolled patients under 18 years of age	

Primary: Dose Limiting Toxicities

End point title	Dose Limiting Toxicities[1]

End point description:

The occurrence/non-occurrence of dose limiting toxicities (DLTs) in the trial defined assessment period. A DLT is defined as any toxicity which is dose limiting, is not attributable to the disease or disease-related processes under investigation, and is considered at least possibly related to either of the investigational medicinal products (IMPs), as defined in the protocol.

End point type	Primary

End point timeframe:

DLTs will be assessed from the first dose on Cycle 1 Day 1 up until Cycle 1 Day 28 during Phase I only.

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: Primary Objective to define the recommended phase II dose (RP2D) of selumetinib/dexamethasone combination in adult and paediatric patients with relapsed/refractory RAS pathway mutant ALL. Modified 2-stage Bayesian Continual Reassessment Method (CRM) was used to determine the maximum tolerated dose independently for each patient group based on the occurrence/non-occurrence of DLT. Dose decision was then made by the Trial Safety Committee. The CRM Dose Decision endpoint is the statistical analysis

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: Events	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: CRM Dose Decision

End point title	CRM Dose Decision[2]

End point description:

The trial target rate of DLT is 0.17 (17%).

For Group A: Dose level 0 has the closest posterior probability estimate (0.154) to this target rate of 0.17. Therefore, the modified Continual Reassessment Method
(CRM) recommended dose level 0 for future adult patients (Group A).

For Group P: Dose level -1 has the closest posterior probability estimate (0.207) to this target rate of 0.17. Therefore, the modified Continual Reassessment Method

(CRM) recommended dose level -1 for future paediatric patients (Group P).

End point type	Primary

End point timeframe:

DLTs will be assessed from the first dose on Cycle 1 Day 1 up until Cycle 1 Day 28 during Phase I only.

Notes:

[2] - 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: Primary Objective to define the recommended phase II dose (RP2D) of selumetinib/dexamethasone combination in adult & paediatric patients with relapsed/refractory RAS pathway mutant ALL. Modified 2-stage Bayesian Continual Reassessment Method (CRM) was used to determine the maximum tolerated dose independently for each patient group based on occurrence/non-occurrence of DLT. Dose decision was then made by Trial Safety Committee. This result of posterior probability is the statistical analysis.

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: Posterior Probability				
number (confidence interval 95%)	0.154 (0.02 to 0.41)	0.207 (0.022 to 0.52)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response

End point title	Response

End point description:

Response to treatment assessed by complete remission rate at 28 days as measured by morphological and minimal residual disease (MRD) response in bone marrow (BM) and for patients with CNS involvement only clearance of Cerebrospinal Fluid (CSF) blasts at 28 days

End point type	Secondary

End point timeframe:

Response at Cycle 1 Day 28

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: Patients				
CR: Complete Remission	1	1		
CRi: Complete remission incomplete platelet recov.	2	0		
PR: Partial remission	0	0		
NR: No response	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - AUC

End point title	Pharmacokinetics - AUC

End point description:

PK of Selumetinib in combination with dexamethasone

End point type	Secondary

End point timeframe:

Cycle 1 Day 4 and Cycle 2 Day 1

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[3]	4[4]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 4	4418 (± 936)	1407 (± 1158)		
Cycle 2 Day 1	4872 (± 2447)	1649 (± 1058)		

Notes:

[3] - Cycle 2 Day 1 subjects: 5

[4] - Cycle 2 Day 1 subjects: 3

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - CMax

End point title	Pharmacokinetics - CMax

End point description:

PK of Selumetinib in combination with dexamethasone

End point type	Secondary

End point timeframe:

Cycle 1 Day 4 and Cycle 2 Day 1

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[5]	4[6]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 4	1512 (± 577)	474 (± 335)		
Cycle 2 Day 1	1097 (± 442)	515 (± 341)		

Notes:

[5] - Cycle 2 Day 1 subjects: 5

[6] - Cycle 2 Day 1 subjects: 3

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - TMax

End point title	Pharmacokinetics - TMax

End point description:

PK of Selumetinib in combination with dexamethasone

End point type	Secondary

End point timeframe:

Cycle 1 Day 4 and Cycle 2 Day 1

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[7]	4[8]		
Units: h				
arithmetic mean (standard deviation)				
Cycle 1 Day 4	1.11 (± 0.31)	1.95 (± 0.07)		
Cycle 2 Day 1	1.80 (± 1.30)	1.60 (± 0.61)		

Notes:

[7] - Cycle 2 Day 1 subjects: 5

[8] - Cycle 2 Day 1 subjects: 3

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - THalf

End point title	Pharmacokinetics - THalf

End point description:

PK of Selumetinib in combination with dexamethasone

End point type	Secondary

End point timeframe:

Cycle 1 Day 4 and Cycle 2 Day 1

End point values	Group A	Group P		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[9]	4[10]		
Units: h				
arithmetic mean (standard deviation)				
Cycle 1 Day 4	1.85 (± 0.31)	1.30 (± 0.14)		
Cycle 2 Day 1	2.50 (± 0.70)	2.37 (± 0.87)		

Notes:

[9] - Cycle 2 Day 1 subjects: 5

[10] - Cycle 2 Day 1 subjects: 3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All medical occurrences which meet the definition of an AE should be reported from the date of commencement of protocol defined treatment until 28 days after the administration of the last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Group A

Reporting group description:

Group A enrolled patients who are 18 years or older

Reporting group title	Group P

Reporting group description:

Group P enrolled patients under 18 years of age

Serious adverse events	Group A	Group P	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	3 / 4 (75.00%)	
number of deaths (all causes)	7	4	
number of deaths resulting from adverse events	4	1	
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peripheral motor neuropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter related infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other: Buttock Abscess			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other: Neutropenic sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other: Right sided pneumonia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 4 (50.00%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	1 / 2	1 / 1	
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A	Group P	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	4 / 4 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	3	
Vascular access complication			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Edema face			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Edema limbs			
subjects affected / exposed	3 / 7 (42.86%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Fatigue			

subjects affected / exposed	4 / 7 (57.14%)	0 / 4 (0.00%)	
occurrences (all)	15	0	
Fever			
subjects affected / exposed	3 / 7 (42.86%)	2 / 4 (50.00%)	
occurrences (all)	10	6	
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Dyspnea			
subjects affected / exposed	3 / 7 (42.86%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Right sided pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Euphoria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Insomnia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Low mood			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)	1 / 4 (25.00%)	
occurrences (all)	8	16	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	1	11	
Blood bilirubin increased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 4 (50.00%)	
occurrences (all)	1	8	
Electrolyte disturbance			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
GGT increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Ldh increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	13	
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	4	10	
Platelet count decreased			
subjects affected / exposed	3 / 7 (42.86%)	2 / 4 (50.00%)	
occurrences (all)	18	11	
Weight gain			

subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
White blood cell decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	5	10	
White cell count increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	5	
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	3	1	
Hydrocephalus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Peripheral motor neuropathy			

subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	15	0	
Proximal myopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tremor			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
ALT increase			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Anemia			
subjects affected / exposed	4 / 7 (57.14%)	3 / 4 (75.00%)	
occurrences (all)	28	14	
Cytopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Deranged clotting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Febrile neutropenia			
subjects affected / exposed	2 / 7 (28.57%)	2 / 4 (50.00%)	
occurrences (all)	5	12	
Ggt			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Thrombotic thrombocytopenic purpura			

subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Papilledema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	2 / 4 (50.00%)	
occurrences (all)	2	3	
Anal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Bloating			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	12	1	
Diarrhea			
subjects affected / exposed	2 / 7 (28.57%)	2 / 4 (50.00%)	
occurrences (all)	5	3	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	3	
Esophagitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hard stool			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Increased appetite			

subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Malabsorption			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	10	
Mucositis oral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	9	
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	1	2	
Stomach pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	1 / 4 (25.00%)	
occurrences (all)	3	2	
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Liver dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Alopecia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Buccal mucosa erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dry ski			

subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Face and neck red			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Petechial rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pressure sore			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	3 / 7 (42.86%)	1 / 4 (25.00%)	
occurrences (all)	10	1	
Renal and urinary disorders			
Jaundice			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 7 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	1	
Renal dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Urinary tract pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Endocrine disorders			
Cushingoid			

subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	2	
Generalized muscle weakness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Mild cramps in hand			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Muscle weakness lower limb			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Proximal myopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Shoulder pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Bacteremia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Buttock abscess			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Catheter related infection			

subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Mouth ulcer			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Mouth ulcers - possible viral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Mucosal infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Oral infection: candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Papulopustular rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Paronychia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Sepsis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 4 (50.00%)	
occurrences (all)	1	3	
Sepsis due to relapsed all			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Upper respiratory infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Urinary tract infection			

subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 4 (0.00%)	
occurrences (all)	19	0	
Hypoalbuminemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	6	
Hypokalemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	7	
Hypomagnesemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	7	
Hyponatremia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 4 (25.00%)	
occurrences (all)	14	2	
Hypophosphatemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	10	
Reduced oral intake			
subjects affected / exposed	0 / 7 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2017	SA01: Protocol version 2.0 Submission to ethics committee to address changes made for the initial competent authority approval. Clairification of DLTs, contraception/pregnancy and associated eligibility criteria, dose rationale, risk mitigation startegy for AEs identified in Selumetinib IB.
25 October 2017	SA02: Protocol version 3.0 Various minor changes and corrections throughout protocol including changes and clarifications to schedule of events, eligibility criteria, outcome measures and IMP details.
26 January 2018	SA03: Protocol version 4.0 Change of Chief Investigator, coinvestigators, and trial management staff and updated contact details.
14 December 2018	SA07: Protocol version 5.0 Urgent Safety Measure to reduce dexamethasone dose in cycle 1 for Group A.
01 May 2019	SA10: Protocol version 6.0 Urgent Safety Measure to reduce dexamethasone dose in cycle 1 for Group P and mandate fluoroquinolone prophylaxis during cycle 1 for all patients.
09 September 2019	SA11: Protocol version 7.0 Urgent Safety Measure to amend dexamethasone dosing schedule from continuous to pulsed in cycle 1, to mandate fluoroquinolone prophylaxis during cycle 1 and 2 and to mandate co-trimoxazole prophylaxis during the trial for all patients.
29 November 2019	SA13: Protocol version 8.0 Changes and clarifications to schedule of events and sampling. Addition of possibility of continued access beyond 6 cycles of treatment. Other minor corrections/amendments.
22 March 2020	SA15: Protocol version 9.0 Clarification of screening process for central RAS mutation testing and Trial Office approved local testing throughout, and Inclusion of additional RAS-pathway activating mutations (NF1, BRAF, IKZF2, IKZF3, IL7Rα or JAK1) tested for locally that can be used for eligibility. Other minor corrections/amendments.

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.

Trial terminated early from poor recruitment, due to a change in the standard of care for this patient population with the use of CAR-T cells.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35246426