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SeluDex: an international trial of selumetinib in combination with dexamethasone for the treatment of acute lymphoblastic leukaemia

Submission date 22/01/2018	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 23/05/2018	**Overall study status** Completed	
Last Edited 28/04/2025	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-selumetinib-and-dexamethasone-for-acute-lymphoblastic-leukaemia-seludex

Study website
https://www.birmingham.ac.uk/seludex

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2016-003904-29

IRAS number

ClinicalTrials.gov number
NCT03705507

Secondary identifying numbers
33990, RG_16-186

Study information

Scientific Title
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

Acronym
SeluDex

Study objectives
The purpose of this trial is to test a new drug called selumetinib in combination with another drug called dexamethasone. The trial specifically targets those patients who have relapsed or refractory acute lymphoblastic leukaemia (ALL) and who have an identified mutation in a particular gene in their cancer’s DNA (in the RAS pathway). The trialists would like to see what effect combining these two drugs has on the patient's leukaemia. This will include looking at how well this treatment works, finding out more information about how it affects the disease, and to see how safe the drugs are in participants taking the trial medication.

During Phase I the trial will look at establishing what is the most suitable dose level of selumetinib in combination with dexamethasone that can be safely given to participants. The Phase II part of the trial will look at the dose level of selumetinib which has already been established in Phase I as being the most effective in combination with dexamethasone to see what effects the combination of these medications will have on participants' leukaemia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire & The Humber - Leeds West Research Ethics Committee, 12/07/2017, ref: 17/YH/0123

Study design
Non-randomized; Interventional; Design type: Treatment, Screening, Drug

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Acute lymphoblastic leukaemia

Interventions
Current intervention as of 15/11/2019:
Patients will receive selumetinib on cycle 1 day 1, then continuously from cycle 1 day 4 onwards. Combined with pulsed doses of dexamethasone on days 2-4, 8-11, 15-18 and 22-25 during cycle 1, then on days 1-4 of cycle two, then on days 1-5 during subsequent cycles. Dose levels will be determined throughout phase I using a statistical model, observation of dose limiting toxicities, and pharmacokinetic analysis. Phase II patients will be administered the recommended phase II dose determined from the phase I part of the trial using the same schedule. The aim is to recruit patients to both phases into both arms of the trial over a 2-year period. It is anticipated that patients will be on treatment for approximately 6 months and will be followed up for a further month after completion of treatment.

Previous intervention:
Patients will receive selumetinib on cycle 1 day 1, then continuously from cycle 1 day 4 onwards, combined with dexamethasone from days 2-28 during cycle 1, then tapered dosing for the first week of cycle two, with full doses on days 1-5 during subsequent cycles. Dose levels will be determined throughout phase I using a statistical model, observation of dose limiting toxicities, and pharmacokinetic analysis. Phase II patients will be administered the recommended phase II dose determined from the phase I part of the trial using the same schedule. The aim is to recruit patients to both phases into both arms of the trial over a two-year period. It is anticipated that patients will be on treatment for approximately six months and will be followed up for a further month after completion of treatment.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Selumetinib

Primary outcome measure
Phase I:
Selection of the Recommended Phase II Dose using occurrence/non-occurrence of dose-limiting toxicities and pharmacokinetic results during cycle 1 day 1-28

Phase II:
Response to treatment is measured using morphological response and for patients with CNS involvement only clearance of CSF blasts at cycle 1 day 28

Secondary outcome measures
Phase I:
1. The occurrence of adverse events (AEs) is measured using Common Terminology Criteria for Adverse Events (CTCAE) version 4 and causality assessment from cycle 1 day 1 until 28-day follow-up
2. Pharmacokinetic variables of selumetinib in combination with dexamethasone are measured using the concentration time profile (area under the curve (AUC), Cmax, Tmax, t1/2) at cycle 1 day 1, cycle 1 day 4 and cycle 2 day 1
3. Response to treatment is measured by complete remission rate using 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 cycle 1 day 28
4. Difference in pharmacokinetics of selumetinib measured by the area under the curve (AUC) when selumetinib is administered as a single agent and in combination with dexamethasone at cycle 1 day 1, cycle 1 day 4 and cycle 2 day 1

Phase II:
1. The occurrence of adverse events (AEs) measured using Common Terminology Criteria for Adverse Events (CTCAE) version 4 and causality assessment from cycle 1 day 1 until 28-day follow-up
2. The occurrence/non-occurrence of DLTs measured by assessment of the DLTs defined in the trial protocol during cycle 1 day 1-28
3. Pharmacokinetic variables of selumetinib in combination with dexamethasone measured using the concentration time profile (area under the curve (AUC), Cmax, Tmax, t1/2) at cycle 1 day 1, cycle 1 day 4 and cycle 2 day 1
4. Difference in pharmacokinetics of selumetinib measured by the area under the curve (AUC) when selumetinib is administered as a single agent and in combination with dexamethasone at cycle 1 day 1, cycle 1 day 4 and cycle 2 day 1
5. MRD response in BM is measured using the MRD level at cycle 1 day 28

Overall study start date
09/10/2014

Completion date
01/08/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 23/12/2021:

1. Morphologically proven relapsed/refractory (M2 or M3 marrow; ≥1st relapse for adults, ≥2nd relapse in paediatric group) or progressive B cell precursor or T-Acute Lymphoblastic Leukaemia (ALL) with demonstrated RAS pathway activating mutations (NRAS, KRAS, FLT3, PTPN11, cCBL, NF1, BRAF, IKZF2, IKZF3, IL7Rα or JAK1) identified during the trial screening process
2. B cell precursor patients must either:
2.1 Have received CAR-T cell therapy, or

2.2. Be awaiting CAR-T cell therapy, or
2.3. Be considered ineligible for CAR-T cell therapy
3. Group P (paediatric): <18 years of age; Group A (adult): ≥18 years of age
4. Adequate renal function:
4.1. Group A: Serum creatinine <1.5 x upper limit of normal (ULN)
4.2. Group P as follows:
4.2.1. ≤5 years: Serum creatinine <0.8 mg/dL or 70 µmol/L
4.2.2. >5 years but ≤ 10 years: Serum creatinine <1 mg/dL or 88 µmol/L
4.2.3. >10 years but ≤ 15 years: Serum creatinine <1.2 mg/dL or 106 µmol/L
4.2.4. >15 years: Serum creatinine <1.5 mg/dL or 132 µmol/L
5. Patient is able to swallow selumetinib capsules whole
6. Performance status (PS): Group A - Eastern Cooperative Oncology Group (ECOG) ≤2; Group P - Lansky play scale ≥60% or Karnofsky scale ≥60%
7. Women of childbearing potential must have a negative pregnancy test
8. Patients who are women of childbearing potential and male patients with partners who are women of childbearing potential must agree to use appropriate contraception whilst on trial
9. Written informed consent
10. Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the trial protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
11. Patients who relapse or progress after HSCT need to be at least at day +100, with no signs of Graft versus Host Disease and off immunosuppressive therapy for at least one week
12. Patients who relapse or progress after CAR T cell therapy should be at least 4 weeks after infusion of CAR T cells.
13. Patients must have a body surface area (BSA) ≥ 0.55 m^2

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Previous inclusion criteria:

1. Morphologically proven relapsed/refractory (M2 or M3 marrow; ≥1st relapse for adults, ≥2nd relapse in paediatric group) or progressive B cell precursor or T-Acute Lymphoblastic Leukaemia (ALL) with demonstrated RAS pathway activating mutations (NRAS, KRAS, FLT3, PTPN11, cCBL) identified during the trial screening process
2. Group P (paediatric): <18 years of age; Group A (adult): ≥18 years of age
3. Adequate renal function:
3.1. Group A: Serum creatinine <1.5 x upper limit of normal (ULN)
3.2. Group P as follows:
3.2.1. ≤ 5 years: Serum creatinine <0.8 mg/dL or 70 µmol/L
3.2.2. > 5 years but ≤ 10 years: Serum creatinine <1 mg/dL or 88 µmol/L
3.2.3. > 10 years but ≤ 15 years: Serum creatinine <1.2 mg/dL or 106 µmol/L
3.2.4. > 15 years: Serum creatinine <1.5 mg/dL or 132 µmol/L
4. Patient is able to swallow selumetinib capsules whole
5. Performance status (PS): Group A - Eastern Cooperative Oncology Group (ECOG) ≤2 (Appendix 6); Group P - Lansky play scale ≥60% or Karnofsky scale ≥60%
6. Women of childbearing potential must have a negative pregnancy test
7. Patients who are women of childbearing potential and male patients with partners who are women of childbearing potential must agree to use appropriate contraception whilst on trial
8. Written informed consent
9. Absence of any psychological, familial, sociological or geographical factors potentially hampering compliance with the trial protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

10. Patients who relapse or progress after HSCT need to be at least at day +100, with no signs of Graft versus Host Disease and off immunosuppressive therapy for at least one week
11. Patients who relapse or progress after CAR T cell therapy should be at least 4 weeks after infusion of CAR T cells.
12. Patients must have a body surface area (BSA) ≥ 0.55 m2

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 42; UK Sample Size: 31; International Sample Size: 11

Key exclusion criteria
Current exclusion criteria as of 23/12/2021:

1. ALL without presence of RAS-pathway activating mutations
2. Mature B-cell leukaemia and Philadelphia positive ALL
3. Prior exposure to MEK, RAS or RAF inhibitors
4. Any unresolved toxicity > = CTCAE Grade 2 from previous anti-cancer therapy, except for alopecia
5. Cardiac conditions as follows:
Group A and P
5.1. Prior or current cardiomyopathy including but not limited to the following:
5.1.1. Known hypertrophic cardiomyopathy
5.1.2. Known arrhythmogenic right ventricular cardiomyopathy
5.2. Even if full recovery has occurred, previous moderate or severe impairment of left ventricular systolic function (LVEF < 45% on ECHO in Group A; SF < 29% in Group P but excluding transient impairments due to e.g. anaemia/sepsis or results not thought to represent a true reflection of cardiac function)
5.3. Severe valvular heart disease
5.4. Severe congential heart disease
5.5. Uncontrolled hypertension:
Group A: BP > = 150/95 mmHg despite medical therapy;
Group P: BP > = 95th percentile for age, height and gender (please refer to Blood Pressure by Age and Height Percentiles tables
Group A
5.6. Baseline (LVEF) below the lower limit of normal (LLN) or < 55% measured by ECHO
5.7. Acute coronary syndrome within 6 months prior to trial registration
5.8. Uncontrolled Angina - Canadian Cardiovascular Society grade II-IV despite medical therapy
5.9. Symptomatic heart failure New York Heart Association (NYHA) Class II-IV, prior or current cardiomyopathy, or severe valvular heart disease
5.10. Prior or current cardiomyopathy including but not limited to the following:

5.10.1. Known hypertrophic cardiomyopathy
5.10.2. Known arrhythmogenic right ventricular cardiomyopathy
5.11. Atrial fibrillation with a ventricular rate > 100 bpm on Electrocardiogram (ECG) at rest
5.12. QTcF > 450ms in male patients or > = 460ms in female patients, or other factors that increase the risk of QT prolongation
Group P
5.13. Baseline SF < 29%
5.14. Atrial fibrillation with a ventricular rate > 130 bpm on Electrocardiogram (ECG) at rest
5.15. QTcF > 450ms in patients < 12 years or > = 460ms in patients > = 12 but < 18 years
6. Ophthalmological conditions as follows:
6.1. Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR) or retinal vein occlusion (RVO)
6.2. Intraocular pressure (IOP) > 21 mmHg or uncontrolled glaucoma (irrespective of IOP)
7. Pregnant and breast feeding females
8. Known severe hypersensitivity to selumetinib, dexamethasone or combination medications or any excipient of these medicinal products, or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib
9. Have received or are receiving an IMP or other systemic anti-cancer treatment (not including dexamethasone, prednisilone, or hydroxycarbamide) within 4 weeks (6 weeks for nitrosoureas, mitomycin, and suramin) prior to trial registration, or within a period during which the IMP or systemic anticancer treatment has not been cleared from the body (e.g. a period of 5 'half-lives'), whichever is the most appropriate and as judged by the investigator
10. Have had recent major surgery within a minimum 4 weeks prior to trial registration, with the exception of surgical placement of vascular access
11. Have received radiation therapy within 4 weeks prior to trial registration, or limited field of radiation for palliation within 7 days of the first dose of trial treatment
12. Laboratory values as listed below (SI units):
12.1. Serum bilirubin > 1.5 x ULN (unless due to Gilbert's syndrome)
13. Have evidence of any other significant clinical disorder or laboratory finding that, as judged by the investigator, makes it undesirable for the patient to participate in the trial
14. Have any evidence of a severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, cardiac, hepatic, or renal disease, active infection (including hepatitis B, hepatitis C, HIV), active bleeding diatheses, or renal transplant)
15. Have refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory bowel disease), or significant bowel resection that would adversely affect the absorption /bioavailability of the orally administered trial medication
16. Any other active malignancy which, in the opinion of the investigator would limit the ability of the patient to complete the study

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Previous exclusion criteria:

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3. Prior exposure to MEK, RAS or RAF inhibitors
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5.2. Even if full recovery has occurred, previous moderate or severe impairment of left ventricular systolic function (LVEF < 45% on ECHO in Group A; SF < 29% in Group P but excluding transient impairments due to e.g. anaemia/sepsis or results not thought to represent a true reflection of cardiac function)
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7. Pregnant and breast feeding females
8. Known severe hypersensitivity to selumetinib, dexamethasone or combination medications or any excipient of these medicinal products, or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib
9. Have received or are receiving an IMP or other systemic anti-cancer treatment (not including dexamethasone or hydroxycarbamide) within 4 weeks (6 weeks for nitrosoureas, mitomycin, and suramin) prior to trial registration, or within a period during which the IMP or systemic anticancer treatment has not been cleared from the body (e.g. a period of 5 ‘half-lives’), whichever is the most appropriate and as judged by the investigator
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12.1. Serum bilirubin > 1.5 x ULN (unless due to Gilbert’s syndrome)
13. Have evidence of any other significant clinical disorder or laboratory finding that, as judged by the investigator, makes it undesirable for the patient to participate in the trial
14. Have any evidence of a severe or uncontrolled systemic disease (e.g. unstable or uncompensated respiratory, cardiac, hepatic, or renal disease, active infection (including hepatitis B, hepatitis C, HIV), active bleeding diatheses, or renal transplant)
15. Have refractory nausea and vomiting, chronic gastrointestinal diseases (e.g., inflammatory

bowel disease), or significant bowel resection that would adversely affect the absorption /bioavailability of the orally administered trial medication
16. Any other active malignancy which, in the opinion of the investigator would limit the ability of the patient to complete the study

Date of first enrolment
18/05/2018

Date of final enrolment
31/01/2023

Locations

Countries of recruitment
Denmark

England

Netherlands

Scotland

United Kingdom

Study participating centre
Freeman Hospital
Freeman Rd
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Great North Children's Hospital
Royal Victoria Infirmary
Queen Victoria Rd
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Birmingham Children's Hospital
Steelhouse Ln

Birmingham
United Kingdom
B4 6NH

Study participating centre
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Birmingham
United Kingdom
B15 2TH

Study participating centre
Alder Hey Children's Hospital Liverpool
East Prescot Road
Liverpool
United Kingdom
L14 5AB

Study participating centre
Royal Marsden Hospital
Downs Rd
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United Kingdom
SM2 5PT

Study participating centre
University College London Hospital
Gower St
Bloomsbury
London
United Kingdom
WC1E 6BT

Study participating centre
Christie Hospital
Wilmslow Rd
Manchester
United Kingdom
M20 4BX

Study participating centre
Royal Hallamshire Hospital
Glossop Rd
Sheffield
United Kingdom
S10 2JF

Study participating centre
Great Ormond Street Hospital
Great Ormond Street
Holborn
London
United Kingdom
WC1N 3JH

Study participating centre
Hammersmith Hospital
Du Cane Rd
White City
London
United Kingdom
W12 0HS

Study participating centre
King's College Hospital
Denmark Hill
Camberwell
London
United Kingdom
SE5 9RS

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre

Prinses Máxima Centrum
Heidelberglaan 25
Utrecht
Netherlands
3584 CS

Study participating centre
University Hospital Rigshospitalet
Blegdamsvej 9
Copenhagen
Denmark
DK-2100

Sponsor information

Organisation
University of Birmingham

Sponsor details
-
Birmingham
England
United Kingdom
-
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seludex@trials.bham.ac.uk

Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)

AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Funder Name
Cancer Research UK; Grant Codes: C27943/A22304

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a peer reviewed journal.

Intention to publish date
31/12/2024

Individual participant data (IPD) sharing plan
Current individual participant data (IPD) sharing statement as of 27/01/2022:
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. The CRCTU is committed to responsible and controlled sharing of anonymised clinical trial data with the wider research community to maximise potential patient benefit while protecting the privacy and confidentiality of trial participants. Data anonymised in compliance with the Information Commissioners Office requirements, using a procedure based on guidelines from the MRC Methodology Hubs, will be available for sharing with researchers outside of the trials team within 6 months of the primary publication. More detailed information on the CRCTU's Data Sharing Policy and the mechanism for obtaining data can be found on the CRCTU website: https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/index.aspx.

Previous individual participant data (IPD) sharing statement:
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository (https://www.cancertrials.bham.ac.uk/SeluDexLive). Type of data that will be shared: case report form data. When the data will become available and for how long: from trial entry registration until the end of the trial. Access to the eRDC system will be granted to authorised individuals via the UK Coordinating Centre, for analysis of outcome measures, Phase I dose escalation continual reassessment method, Phase II Bayesian design. Consent from participants was obtained prior to trial entry,

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		04/03/2022	07/03/2022	Yes	No
HRA research summary			28/06/2023	No	No
Basic results	version 1.0	17/04/2025	28/04/2025	No	No
Statistical Analysis Plan	version 2.0	09/09/2019	28/04/2025	No	No