

BMJ Open Selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult acute lymphoblastic leukaemia (SeluDex): study protocol for an international, parallel-group, dose-finding with expansion phase I/II trial

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ABSTRACT

Introduction Event-free survival rates at 15 years for paediatric patients with relapsed/refractory acute lymphoblastic leukaemia (ALL) are 30%–50%, with 5-year survival for adult patients only 20%. Many patients with newly diagnosed and relapsed ALL harbour somatic RAS-signalling activation mutations. Induction therapy for ALL involves steroids, with preclinical data suggesting the combination of dexamethasone with the MEK1/2 inhibitor, selumetinib (ARRY-142886) has a synergistic anticancer effect.

Methods and analysis The SeluDex trial is an international, parallel-group, dose-finding with expansion, phase I/II trial to assess the selumetinib/dexamethasone combination in adult and paediatric patients with relapsed/refractory, RAS pathway mutant ALL. The Cancer Research UK Clinical Trials Unit at University of Birmingham is the UK Coordinating Centre, with national hubs in Copenhagen, Denmark; Monza, Italy; Münster, Germany; Paris, France; and Utrecht, Netherlands. Patients with morphologically proven relapsed/refractory or progressive B-cell precursor or T-cell ALL, with demonstrated RAS pathway activating mutations are eligible. Adult patients are ≥ 18 years old, ECOG ≤ 2 and paediatric < 18 years old, Lansky play scale $\geq 60\%$ or Karnofsky score $\geq 60\%$. Phase I primary objective is the recommended phase II dose of selumetinib as defined by occurrence/non-occurrence of dose limiting toxicities using the continual reassessment method; phase II will evaluate preliminary antileukaemic activity of the combination, as defined by morphological response 28 days post-treatment using a Bayesian approach. Target recruitment is between 26 and 42 patients (minimum 13 and maximum 21 per group), depending the number of phase I patients included in phase II.

Strengths and limitations of this study

- Novel combination of the MEK1/2 inhibitor, selumetinib, with dexamethasone.
- Seamless phase I/II Bayesian trial design with a continual reassessment method for dose escalation in phase I.
- Parallel cohort trial design of adult and paediatric patients within one protocol.
- Availability of CAR T-cell therapy since this trial started recruitment has competed for the same patient population, however, SeluDex offers a bridging treatment option for patients awaiting CAR T-cell therapy outside clinical studies or at relapse after CAR-T treatment.

Ethics and dissemination Medical ethical committees of all the participating countries have approved the study protocol; initial (UK) ethics approval (17/YH/0123) was granted by Yorkshire & The Humber—Leeds West Research Ethics Committee. Participants are required to provide written informed consent/assent. Results will be disseminated through national and international presentations and peer-reviewed publications.
Trial registration number ISRCTN92323261.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer, representing 26.8% of all childhood malignancies.¹ While the overall cure rate for newly diagnosed paediatric ALL is approaching 90%, children with relapsed ALL (rALL) are still

facing a poor outlook, with reported overall event-free survival rates at 15 years of 30%–50%,² and rALL remains a frequent cause of death.

In adults, the frequency of ALL is significantly lower, with an incidence of around one per 100 000.³ ALL in adulthood has proven to be more challenging to treat compared with childhood ALL, with the disease being more resistant to chemotherapy, and patients have a reduced treatment tolerance especially in the elderly population. Five-year overall survival rate remains at ~20% among adult patients aged ≥ 60 years, even though improvement has been observed since 1980.⁴

Data demonstrate that mutations activating the RAS-signalling cascade (NRAS, KRAS, FLT3 and PTPN11 and cCBL) are highly prevalent at both diagnosis and relapse of paediatric B-cell precursor ALL (incidence 38% at relapse), and are associated with high-risk features such as early relapse, central nervous system (CNS) involvement and chemoresistance.⁵ Neurofibromin (NF1) copy number variants, point mutations or intragenic deletions have been reported in approximately 4% of T-cell ALL, 14% of early T-cell precursor (ETP), ~30% of low hypodiploidy, 2% high risk of B-cell ALL and 75% of relapsed hypodiploid ALL.^{6–10} BRAF point mutation incidence is approximately 3% in T-cell ALL, 4% in ETP and 0.5% in high-risk B-cell ALL.^{7–9} IKZF2 and IKZF3 deletions which have recently been shown to activate the RAS-pathway have an incidence of approximately 18% in hypodiploid ALL.¹¹ IL7R α point mutations, deletions and in-frame alterations are found in approximately 9% of T-ALL,^{12 13} and JAK1 point mutations are found in approximately 5% of T-ALL.¹⁴

Selumetinib is a potent and selective allosteric MEK1/2 inhibitor that has been evaluated in phase II/III clinical trials for several cancers, including BRAF mutation-positive melanoma,¹⁵ metastatic uveal melanoma,¹⁶ pancreatic,¹⁷ colorectal¹⁸ and KRAS mutation-positive NSCLC.¹⁹ Preclinical models suggest a synergistic effect when selumetinib and dexamethasone were combined in an orthotopic mouse model with three different RAS-pathway mutant ALL primografts and a mechanistic basis to the synergy was identified involving heightened levels of the proapoptotic BIM protein.²⁰ However, the combination of selumetinib and dexamethasone has not been evaluated in a clinical trial setting.

The aim of the SeluDex trial is to determine the dose of selumetinib to use in combination with dexamethasone in adult and paediatric patient populations, and to assess the preliminary antileukaemic properties of the combination in each group of patients.

METHODS AND ANALYSIS

Study design

The SeluDex trial is a parallel-group, non-randomised, open-label, dose-finding with expansion, phase I/II clinical trial. As an early phase dose-finding and signal-seeking trial, a comparator arm was not included. Group A (adult

patients) and group P (paediatric patients) will both receive selumetinib in combination with a standard dose of dexamethasone (figure 1). Patients will be recruited from public hospitals. The Cancer Research UK Clinical Trials Unit (CRCTU) at University of Birmingham is the UK Coordinating Centre, with national hubs in Copenhagen, Denmark; Monza, Italy; Münster, Germany; Paris, France; and Utrecht, Netherlands. The national coordinating and participating centres are all part of the Innovative Therapies for Children with Cancer in Europe consortium (ITCC).

This trial aims to recruit between 26 and 42 patients (minimum of 13 and maximum of 21 in each group), depending on how many phase I patients are included also in phase II. The recruitment period is expected to be 4 years, with participants followed up for 1 month after a maximum of 6 treatment cycles. WHO Trial Registration Data Set is attached in online supplemental appendix 1.

Patient and public involvement

Patients and public were not involved in the design and conduct of this research but will be consulted in the reporting and dissemination of its outputs.

Patient selection

The two parallel patient groups in SeluDex, group A (Adult) and P (Paediatric), have similar but discrete eligibility criteria. The main eligibility criteria are detailed in boxes 1 and 2, respectively. The screening process is the same for both groups. Eligibility for trial entry is dependent on screening of a bone marrow (BM) aspirate to confirm morphological relapse and RAS-pathway mutation status. Peripheral blood may also be used in the case of a dry tap if white cell counts $>50 \times 10^9/L$. Centralised genetic analysis in the UK at Northern Genetics Service's laboratories in Newcastle upon Tyne will identify the presence of a RAS-pathway activating mutation (key exons of NRAS, KRAS, FLT3, PTPN11 or cCBL mutation). A primary screen of the two most common mutations (NRAS and KRAS) will be performed first and if no mutations are found a secondary screen of the remaining mutations (FLT3, PTPN11 and cCBL) will be performed. Alternatively, locally obtained genetic results may be used to confer RAS-pathway mutation status if tested in a clinically compliant laboratory using a clinically validated test with material from the current relapse. Laboratories will be approved by the Trial Office to use local NRAS, KRAS, FLT3, PTPN11, cCBL, NF1, BRAF, IKZF2, IKZF3, IL7R α or JAK1 testing.

Consent

Consent is requested by an investigator at two time points. A pretrial genetic assessment consent allows for central/local analysis of a sample at screening to assess RAS mutation status, and the main trial consent, which is performed once mutation status is confirmed and a treatment slot is reserved. The main trial consent will be for either the phase I dose finding, or phase II dose

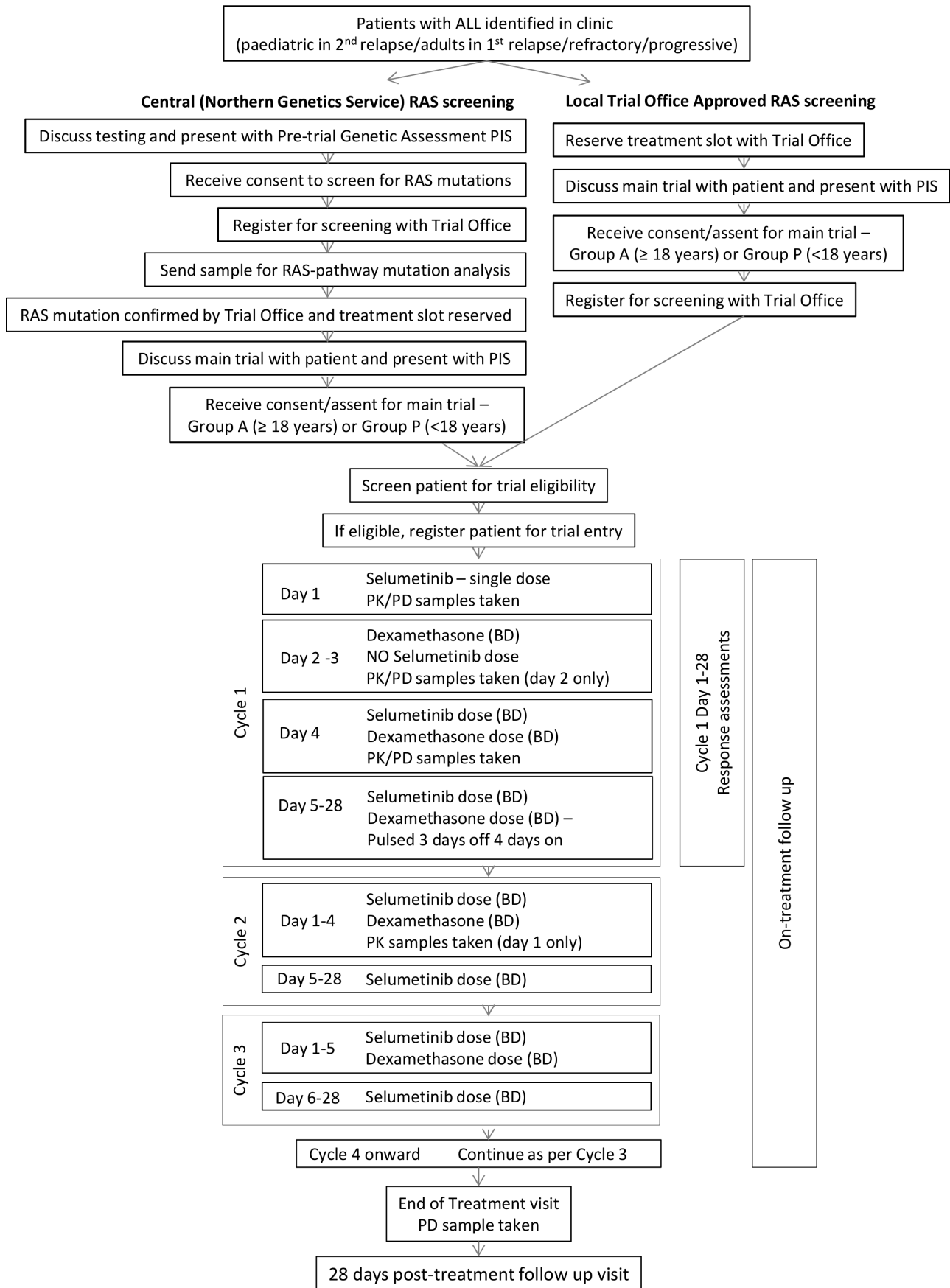


Figure 1 SeluDex trial schema SeluDex trial schema showing the patient pathway highlighting screening, trial entry, treatment and follow-up. ALL, acute lymphoblastic leukaemia; BD, two times a day; PD, pharmacodynamic; PIS, patient information sheet; PK, pharmacokinetic.

Box 1 Main eligibility criteria for Group A

Main inclusion criteria

- ▶ Morphologically proven relapsed/refractory (M2 or M3 marrow; ≥ 1 st relapse) or progressive B cell precursor or T-acute lymphoblastic leukaemia (ALL) with demonstrated RAS pathway activating mutations (NRAS, KRAS, FLT3, PTPN11, cCBL, neurofibromin 1, BRAF, IKZF2, IKZF3, IL7R α or JAK1) identified during the trial screening process.
- ▶ B cell precursor patients must either:
 - Have received CAR-T cell therapy, or
 - Be awaiting CAR-T cell therapy, or
 - Be considered ineligible for CAR-T cell therapy.
- ▶ ≥ 18 years of age.
- ▶ Adequate renal function: Serum creatinine $< 1.5 \times$ upper limit of normal (ULN).
- ▶ Patient is able to swallow selumetinib capsules whole.
- ▶ Eastern Cooperative Oncology Group (ECOG) ≤ 2 .
- ▶ Women of childbearing potential must have a negative pregnancy test.
- ▶ Patients who are women of childbearing potential and male patients with partners who are women of childbearing potential must agree to use appropriate contraception (see section 7.9.3 for definition) while on trial.
- ▶ Written informed consent.
- ▶ Patients must have a body surface area $\geq 0.55 \text{ m}^2$.

Main exclusion criteria

- ▶ ALL without presence of RAS-pathway activating mutations.
- ▶ Mature B-cell leukaemia and Philadelphia positive ALL.
- ▶ Prior exposure to MEK, RAS or RAF inhibitors.
- ▶ Any unresolved toxicity \geq Common Terminology Criteria for Adverse Events grade 2 from previous anticancer therapy, except for alopecia.
- ▶ Cardiac conditions as follows:
 - Prior or current cardiomyopathy including but not limited to the following:
 - Known hypertrophic cardiomyopathy.
 - Known arrhythmogenic right ventricular cardiomyopathy.
 - Even if full recovery has occurred, previous moderate or severe impairment of left ventricular systolic function (LVEF $< 45\%$ on echocardiogram, ECHO).
 - Severe valvular heart disease.
 - Severe congenital heart disease.
 - Uncontrolled hypertension: Blood pressure $\geq 150/95$ mm Hg despite medical therapy.
 - Baseline (LVEF) below the lower limit of normal or $< 55\%$ measured by ECHO.
 - Acute coronary syndrome within 6 months prior to trial registration.
 - Uncontrolled Angina—Canadian Cardiovascular Society grade II–IV despite medical therapy.
 - Symptomatic heart failure New York Heart Association class II–IV, prior or current cardiomyopathy, or severe valvular heart disease.
 - Atrial fibrillation with a ventricular rate > 100 bpm on ECG at rest.
 - QT Interval Corrected Using Fridericia's Formula (QTcF) > 450 ms in male patients or ≥ 460 ms in female patients, or other factors that increase the risk of QT prolongation.

Box 2 Main eligibility criteria for Group B

Main inclusion criteria

- ▶ Morphologically proven relapsed/refractory (M2 or M3 marrow; ≥ 2 nd relapse) 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, IL7R α or JAK1) identified during the trial screening process.
- ▶ B cell precursor patients must either:
 - Have received CAR-T cell therapy, or
 - Be awaiting CAR-T cell therapy, or
 - Be considered ineligible for CAR-T cell therapy.
- ▶ < 18 years of age.
- ▶ Adequate renal function:
 - ≤ 5 years: serum creatinine < 0.8 mg/dL or $70 \mu\text{mol/L}$.
 - > 5 years but ≤ 10 years: serum creatinine < 1 mg/dL or $88 \mu\text{mol/L}$.
 - > 10 years but ≤ 15 years: serum creatinine < 1.2 mg/dL or $106 \mu\text{mol/L}$.
 - > 15 years: serum creatinine < 1.5 mg/dL or $132 \mu\text{mol/L}$.
- ▶ The patient is able to swallow selumetinib capsules whole.
- ▶ Lansky play scale $\geq 60\%$ or Karnofsky scale $\geq 60\%$.
- ▶ Women of childbearing potential must have a negative pregnancy test.
- ▶ Patients who are women of childbearing potential and male patients with partners who are women of childbearing potential must agree to use appropriate contraception (see section 7.9.3 for definition) whilst on trial.
- ▶ Written informed consent.
- ▶ Patients must have a body surface area $\geq 0.55 \text{ m}^2$.

Main exclusion criteria

- ▶ ALL without presence of RAS-pathway activating mutations.
- ▶ Mature B-cell leukaemia and Philadelphia positive ALL.
- ▶ Prior exposure to MEK, RAS or RAF inhibitors.
- ▶ Any unresolved toxicity \geq Common Terminology Criteria for Adverse Events grade 2 from previous anticancer therapy, except for alopecia.
- ▶ Cardiac conditions as follows:
 - Prior or current cardiomyopathy including but not limited to the following:
 - Known hypertrophic cardiomyopathy.
 - Known arrhythmogenic right ventricular cardiomyopathy.
 - Even if full recovery has occurred, previous moderate or severe impairment of left ventricular systolic function (SF $< 29\%$ but excluding transient impairments due to, for example, anaemia/sepsis or results not thought to represent a true reflection of cardiac function).
 - Severe valvular heart disease.
 - Severe congenital heart disease.
 - Uncontrolled hypertension: Blood pressure ≥ 95 th percentile for age, height and gender.
 - Baseline SF $< 29\%$.
 - Atrial fibrillation with a ventricular rate > 130 bpm on ECG at rest.
 - QT Interval Corrected Using Fridericia's Formula (QTcF) > 450 ms in patients < 12 years or ≥ 460 ms in patients ≥ 12 but < 18 years.
- ▶ Ophthalmological conditions as follows:
 - Current or history of retinal pigment epithelial detachment/central serous retinopathy or retinal vein occlusion.

expansion. Furthermore, age-specific consent/assent forms are available for patients over 16 years of age, and parents/legal guardians of paediatric patients (as

Continued

Box 2 Continued

- Intraocular pressure (IOP) >21 mm Hg or uncontrolled glaucoma (irrespective of IOP).
- ▶ Pregnant and breastfeeding females
- ▶ 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 biological composition to selumetinib.

appropriate according to age and national legislation). An example of the main consent form for adult patients is available in online supplemental appendix 2. Age-specific patient information sheets (PISs) are available for patients over 16 years of age, parents/legal guardians of paediatric patients, and teenage patients aged 13–15 years. As an example, the adult PIS is available in online supplemental appendix 3.

Interventions

The dosing schedule for the dose-finding phase of the trial is summarised below for each group and detailed in specified tables. Treatments are given over a 28-day cycle and will be continued for six cycles unless one or more of the following is observed; intolerable toxicity, confirmed disease recurrence or progression, pregnancy, severe non-compliance to protocol, development of any trial-specific criteria for discontinuation (not reaching at least a partial response (PR) at cycle 1, day 28), or investigator decision, for example, if the patient requires a prohibited concomitant medication. The trial schedule of events is included in online supplemental appendix 4.

Group A

Dexamethasone: Steroids are a backbone of all induction blocks of ALL therapy with dexamethasone, the preferred steroid in the management of patients with ALL (table 1). Initially, dexamethasone was to be administered on a continuous dosing schedule with a weekly

total dose of 42 mg/m² for the first course. However, following an observed increase in the risk of infections during the initial stages of the trial, the trial dexamethasone dosing regimen was amended to allow intermittent treatment in blocks rather than continuously, and incorporating a dose reduction from 6 mg/m²/day in cycle 1 (d2–4 and D8–11) to 4 mg/m²/day during D15–18 and D22–25 of cycle 1. Further dexamethasone is given as a low dose in cycle 2 (D1–4 only: 4 mg/m²/day) and then as a high dose again in subsequent cycles (C3–6, D1–5 only: 6 mg/m²/day).

Selumetinib: The dose of 75 mg was chosen as the starting dose for group A (dose Level 0) with the dose only increased if pharmacokinetic (PK) data suggest the addition of dexamethasone decreases selumetinib serum concentrations significantly due to induction of the cytochrome P450 enzyme CYP3A4.²¹

Group P

Dexamethasone: As with adult dosing, trial dexamethasone dosing regimen was amended during the initial stages of the trial to be reduced after the first 2 weeks and to be given pulsed during cycle 1 due to the increase in infection risk (table 2).

Selumetinib: Results of two paediatric phase I trials using selumetinib only^{22 23} gave the maximum tolerated dose (MTD) as 2×25 mg/m²; thus in the SeluDex trial, 20 mg/m² (80% of the single agent MTD of selumetinib) was chosen as the starting dose for safety reasons (dose level -1), specifically for those patients with CNS disease receiving concomitant intrathecal methotrexate.

Treatment compliance

Treatment compliance should be discussed with the patient/parent/legal guardian at the beginning of each cycle when study drug is dispensed. The research nurse should complete the relevant sections including recording the morning and afternoon doses and the dates they are to be taken in the diary. All patients/parents/

Table 1 Group A (≥18 years) dosing schedule in phase I dose finding

Dose level	Selumetinib (% of adult MTD)	Dexamethasone	Initial design
	Cycle 1 D1: single dose Cycle 1 D4–D28: BD dosing Subsequent cycles 2–6: D1–28: two times dosing	Cycle 1 D2–4 and D8–11: 6 mg/m ² /day, D15–18 and D22–25: 4 mg/m ² /day Cycle 2 D1–4: 4 mg/m ² /day Subsequent cycles 3–6, D1–5 only 6 mg/m ² /day	Applicable prior to DLTs
-1	80%	60 mg two times orally	mg/m ² /day orally divided into two doses (as per local practice)
0	100%	75 mg two times orally	n/a
+1†	113%–120%‡	85–90 mg‡ two times orally	Cohorts 1 and 2 Cohorts 3, 4, 5 and 6

*Body surface area for group A to be calculated according to standard institutional practice.

†Important: The selumetinib dose reverts from the +1 dose level to dose level 0 with the start of cycle 2 as patients will only be exposed to a short pulse of dexamethasone which is not expected to substantially affect selumetinib PK.

‡The proposed increase of dose might be changed based on PK results of dose level 0.

DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; n/a, not applicable; PK, pharmacokinetic.

Table 2 Group P (<18 years) dosing schedule in phase I dose finding

Dose level	Selumetinib (% of adult MTD) Cycle 1 D1: single dose Cycle 1 D4–D28: two times dosing Subsequent cycles 2–6: D1–28: two times dosing		Dexamethasone Cycle 1 D2–4 and D8–11: 6 mg/m ² /day, D15–18 and D22–25: 4 mg/m ² /day Cycle 2 D1–4: 4 mg/m ² /day Subsequent cycles 3–6, D1–5 only 6 mg/m ² /day	Initial design Applicable prior to DLTs
–1	80%	20 mg/m ² * two times orally	mg/m ² */day orally divided into two doses (as per local practice)	Cohorts 1 and 2
0	100%	25 mg/m ² * two times orally		Cohorts 3 and 4
+1†	113%–120%‡	28–30 mg‡/m ² * two times orally		Cohorts 5 and 6

*Body surface area for group P to be calculated according to standard institutional practice.

†Important: The selumetinib dose reverts from the +1 dose level to dose level 0 with the start of cycle 2 as patients will only be exposed to a short pulse of dexamethasone which is not expected to substantially affect selumetinib PK.

‡The proposed increase of dose might be changed based on PK results of dose level 0.

DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PK, pharmacokinetic.

legal guardians will be required to complete a diary with the daily time of administration of the study drugs, which must be returned to the clinic for checking at each visit. If a dose is missed, the reason must be noted in the diary by the patient/parent/legal guardian. Patients/parents/legal guardians should be advised to return any unused investigational medicinal product in the original bottles, in addition to returning any empty bottles. Compliance should be reviewed at the end of each cycle by the site staff via review of the patient diary and discussion with the patient/parent/legal guardian that is to be documented in the medical notes.

Dose modifications

No dexamethasone dose reductions are permitted during cycle 1 and 2. If identifiable dexamethasone related intolerable toxicity is present during cycle 3 then a dose reduction to 4 mg/m²/day is allowed from cycle 4 onwards.

Dose modifications for the following selumetinib-related toxicities are allowed:

- ▶ Grade 3 neutropenia with infection and/or fever (granulocyte colony-stimulating factor [G-CSF] is permitted).
- ▶ Grade 3 or 4 nausea, vomiting, or diarrhoea, if persistent despite optimal antiemetic and/or antidiarrhoeal therapy.
- ▶ Any grade 3 or greater non-haematological toxicity.
- ▶ Any other grade 4 haematological toxicity.

If one or more of these are observed the following action should be taken;

First occurrence: Hold selumetinib until recovery to grade <1 or baseline; restart at original dose level.

Second occurrence: Hold selumetinib until recovery to grade <1 or baseline; keep same dose but reduce to once daily.

Third occurrence: Hold selumetinib until recovery to grade <1 or baseline; use 60% of the original dose but go

back to twice daily. For group P: 45 mg reduce to 30 mg; 40 mg to 25 mg; 30–35 mg to 20 mg; 20–25 mg to 10 mg. For group A: 75 mg reduce to 45 mg; 60 mg to 35 mg.

Fourth occurrence: Discontinue selumetinib.

Concomitant medication

Patients should avoid consuming large amounts of grapefruits, seville oranges and any other products that may contain these fruits, for example, grapefruit juice. In addition, patients should not take any vitamin E supplements. Restricted medications are listed in [table 3](#).

Trial outcomes

Phase I

The primary objective for the phase I dose-finding component is to determine the recommended phase II dose (RP2D) of selumetinib in combination with dexamethasone, as defined by the occurrence/non-occurrence of dose limiting toxicities (DLTs) in the trial-defined assessment period. The trial will achieve this through the use of the continual reassessment method (CRM).²⁴ DLTs will be assessed from the first dose on cycle 1, day 1 up until cycle 1, day 28 during phase I only. 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 selumetinib or dexamethasone (see the Dose limiting toxicities section).

Secondary outcomes for the phase I component are:

- ▶ The occurrence of adverse events (AEs) as measured by Common Terminology Criteria for Adverse Events (CTCAE) V.4²⁵ and causality assessment.
- ▶ PK variables of selumetinib in combination with dexamethasone from the concentration time profile (area under the plasma concentration-time curve (AUC), C_{max}, T_{max}, t_{1/2}).

Table 3 Restricted medications within the SeluDex trial

▶ Acetazolamide	▶ Fluconazole	▶ Oral contraceptives
▶ Aminoglutethimide	▶ Fluvoxamine	▶ Oxcarbazepine
▶ Antacids	▶ Glucocorticoids	▶ Phenobarbital
▶ Anticholinesterases	▶ Hypoglycaemic agents, for example, insulin	▶ Phenytoin
▶ Anti-hypertensives	▶ Indinavir	▶ Pioglitazone
▶ Aprepitant	▶ Itraconazole	▶ Prednisolone
▶ Barbiturates	▶ Ketoconazole	▶ Primidone
▶ Beta-naphthoflavone	▶ Loop diuretics	▶ Rifabutin
▶ Carbamazepine	▶ Methylcholanthrene	▶ Rifampicin
▶ Carbenoxolone	▶ Modafinil	▶ Ritonavir
▶ Clarithromycin	▶ Nafcillin	▶ Salicylates
▶ Coumarin anticoagulants	▶ Nefazodone	▶ Saquinavir
▶ Diltiazem	▶ Nelfinavir	▶ Suboxone
▶ Diuretics	▶ Nevirapine	▶ Telithromycin
▶ Efavirenz	▶ Norethindrone	▶ Thiazide diuretics
▶ Ephedrine	▶ Non-steroidal anti-inflammatory drugs (NSAIDs)	▶ Troglitazone
▶ Erythromycin	▶ Omeprazole	▶ Verapamil
		▶ St John's Wort

- ▶ Response to treatment assessed by complete remission (CR) rate at 28 days as measured by morphological and minimal residual disease (MRD) response in BM and for patients with CNS involvement only clearance of cerebrospinal fluid (CSF) blasts at 28 days.
- ▶ Difference in PK of selumetinib (Δ AUC) when selumetinib is administered as single agent and in combination with dexamethasone.

Phase II

The primary objective for the phase II expansion component will be to assess preliminary antileukaemic activity of the selumetinib/dexamethasone drug combination as defined by morphological response (CR, CR with incomplete platelet recovery (CRi), PR, non-response and for patients with CNS involvement only, clearance of CSF blasts) 28 days post-treatment end. Response evaluation will be undertaken with BM response at day 28, including MRD and CSF surveillance for CNS positive patients with standard cytology. A patient will be classified as having a response if they achieve CR or CRi at the day 28 assessment (with an acceptable window of day 15–35).

Secondary outcomes for the phase II component are;

- ▶ The occurrence of AEs as measured by CTCAE V.4 and causality assessment.
- ▶ The occurrence/non-occurrence of DLTs in the trial defined assessment period.
- ▶ PK variables of selumetinib in combination with dexamethasone from the concentration time profile (AUC , C_{max} , T_{max} , $t_{1/2}$).
- ▶ Difference in PK of selumetinib (Δ AUC) when selumetinib is administered as single agent and in combination with dexamethasone.
- ▶ MRD response in BM at 28 days.

Exploratory outcomes of the trial for both phases of the trial include exploratory pharmacodynamic (PD) biomarker studies if clinical responses are observed. These will include levels of phosphorylated ERK by flow

cytometry in leukaemic cells from patients at several time points (cycle 1 day 1, cycle 1 day 4 and end of treatment visit), as well as retrospective mRNA profiling, including the apoptotic initiator Bcl-2-like protein 11 (Bcl2-L-11/BIM).^{20 26}

Dose limiting toxicities

DLTs will be assessed from the first dose in cycle 1 day 1 until cycle 1 day 28 during phase I. A haematological DLT is defined as BM aplasia/hypoplasia, defined as overall marrow cellularity less than 25% (malignant infiltration or other causes are excluded), which does not recover by cycle 1 day 28. This includes an absolute neutrophil count of less than $0.5 \times 10^9/L$ and a non-transfusion dependent platelet count of less than $25 \times 10^9/L$ due to BM aplasia/hypoplasia. In addition, grade 4 febrile neutropenia, and any grade 5 AE are also defined as a haematological DLT.

Non-haematological DLTs in group A are defined as left ventricular ejection fraction $<45\%$ as measured by echocardiogram; and in group P as $>15\%$ reduction in shortening fraction from baseline by echocardiogram. Results must be viewed by a consultant cardiologist to confirm that there has been a genuine deterioration in cardiac function. In addition, any grade 5 AE, grade 3 nausea or vomiting on or before CID28 only which does not resolve to $<$ grade 2 within 48 hours (with or without supportive care), grade 3 mucositis on or before CID28 only which does not resolve to grade <2 within 48 hours (with or without supportive care), any other grade 3 or 4 non-haematological toxicity, specifically excluding: alopecia; dexamethasone related CTCAE grade 3 toxicities (eg, hyperglycaemia, muscle weakness, psychosis, avascular necrosis); tumour lysis syndrome; and increased alanine transaminase or aspartate aminotransferase.

Suspected DLTs will be reviewed and confirmed by the Trial Safety Committee (TSC) during dose decision meetings at the end of each cohort during phase I.

Statistical analysis plan

Both groups (A and P) will be analysed separately for both phases of the trial. If the response rates in the two groups are seen to be similar in the phase II component of the trial, then there may be some consideration to analysing response in the adult and paediatric groups collectively. The phase I evaluable population includes those patients who do not withdraw/die or discontinue treatment due to non-treatment related causes before the end of the DLT assessment period. A patient is evaluable regardless of the above if they experience a DLT. The phase II evaluable population includes all patients who received any treatment. There is no scope to replace unevaluable patients in the trial.

Phase I

The maximum number of patients to be recruited in phase I is 24; 12 into each group in parallel.

The trial will use the CRM to find which doses to take forward to the phase II activity component of the trial for each group respectively. Each group will use a modified two-stage Bayesian CRM,²⁷ recruiting patients in cohorts of two. The design incorporates rules to enable early stopping if the DLT rate at the lowest dose is unacceptably high. Patients are assigned to the starting dose level and follow the initial design (see tables 1 and 2) until the first DLT is observed. Once the first DLT is observed the CRM takes over and determines the 'best' dose level that the next cohort should be assigned to, based on the model-based predicted probabilities of toxicity at each possible dose. The acceptable level of toxicity (probability of a DLT) has been chosen to be 17% for each group, that is, the trial will aim to find the highest dose that coincides with this acceptable level. This value was selected based on discussion with clinicians concerning the acceptable rate of DLTs based on the chosen definition.

The stopping rule for toxicity used in the modified CRM is based on the probability of the true DLT rate at the lowest dose being >27%. If based on the observed data the probability of the true DLT rate being greater than this chosen value is >0.85 then the modified CRM will suggest that the trial should stop. The current MTD estimate is calculated after each cohort has been assessed for the full DLT assessment period and the next cohort of patients are then assigned to this MTD estimate. The final MTD estimate calculated after all 12 patients have been treated is the dose estimate to be considered to be taken forward to the phase II component.

This design works relatively well with computer simulations showing a probability for correctly selecting the right dose level of at least 0.6 when the true dose level is 0 or 1, around 0.5 when the true dose level is -1 and at least 0.6 for stopping early when all doses are truly too toxic.

Data will be reviewed at each dose decision stage by the independent TSC. The TSC will incorporate PK results into the decision process; the CRM will advise as to which doses are safe, with the PK additionally informing if there is a need for escalation/de-escalation.

Phase II

The phase II part of the trial will include patients from the phase I component that were dosed at the RP2D plus patients recruited into the expansion cohort. The number of phase I patients taken forward to the phase II assessment will be at least 4 in each group and the maximum number of patients to be recruited in the expansion cohort will be 9 in each group, giving a total of 13.

Based on data published by the TACL group (CR rate of 44% for second relapses and 27% for third relapses²⁸) and seeing as we expect a mixture of second, third and higher relapses in paediatric patients and similar if not worse relapse rates for adult patients, we estimate the overall response rate on standard treatment to be approximately 35%.

This phase will use a Bayesian approach to investigate the true response rate in each group. A beta-binomial conjugate analysis will be used to create a posterior probability distribution of the true response rate using the observed trial data combined with a beta (1, 1) minimally informative prior. The trial design is based on the decision criteria that if there is a high probability (>0.80) that the true response rate is >35% then this will indicate that the treatment is worthy of further research. With 13 patients, this design works reasonably well with a low probability of 0.08 of incorrectly concluding that the treatment is worthy when the true response rate is only 25% and a high probability of 0.82 of correctly concluding that the treatment is worthy when the true response rate is 55%.

If the response rates are similar in both groups, then information may be borrowed across Groups A and P to provide more accuracy in determining the true response rate for both groups collectively

There are no planned subgroup or interim analyses.

PK and PD samples

Blood samples for PK and PD analysis will be obtained on days 1, 2 and 4 of cycle 1, with blood samples for PK analysis collected again on day 1 of cycle 2, and blood samples for PD analysis obtained at the end of trial treatment.

For PK analysis plasma will be subjected to liquid chromatography-mass spectrometry analysis to quantify concentrations of selumetinib, its major metabolite N-desmethyl selumetinib and dexamethasone. Two types of PD samples will be prepared from peripheral blood samples of patients who have a white cell count >10×10⁹/L; samples will either be fixed on site in BD Lyse Fix solution or collected separately in Blood RNA Preservative Tubes. These PD samples will be transferred to the UK Biobank at the University of Birmingham for storage.

All samples will be collected in accordance with national regulations and requirements including standard operating procedures for logistics and infrastructure. Samples will be taken in appropriately licensed premises, stored and transported in accordance with the Human Tissue Authority guidelines and National Health Service trust policies.

AEs reporting and analysis

The collection and reporting of AEs as measured by CTCAE V.4 will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service. Definitions of different types of AEs are listed in online supplemental appendix 5; this includes abnormal laboratory findings which are considered clinically significant. The reporting period for AEs will be from the date of commencement of protocol defined treatment until 28 days after the administration of the last treatment. The investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol. In addition, DLTs will be assessed for the phase I part of the trial only. All will be reported using the applicable electronic case report form (CRF).

Data management

CRFs can be entered online into the electronic Remote Data Capture system hosted by CRCTU at the University of Birmingham. Authorised staff at sites will require an individual secure login username and password to access this online data entry system. Paper CRFs must be completed, signed and dated, and returned to the SeluDex Trial Office by the investigator or an authorised member of the site research team. Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. All sections are to be completed.

All trial records must be archived and securely retained for at least 25 years. No documents will be destroyed without prior approval from the sponsor, via the SeluDex Trial Office. On-site monitoring will be carried out as required following a risk assessment and as documented in the Quality Management Plan. Any monitoring activities will be reported to the central SeluDex Trial Office and any issues noted will be followed up to resolution. SeluDex will also be centrally monitored, which may trigger additional on-site monitoring. Further information regarding data management is provided in the study protocol.

The CRCTU will hold the final trial dataset and will be responsible for the 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 Medical Research Council Methodology Hubs, will be available for sharing with researchers outside of the trials team within 12 months of the primary publication.

Trial organisation structure

The University of Birmingham will act as sponsor to this international, multicentre study: Research Support Group, Aston Webb Building, Room 119, Birmingham, B15 2TT. Email: researchgovernance@contacts.bham.ac.uk. The trial is being conducted under the auspices of the CRCTU, The University of Birmingham according to their local procedures. The Trial Management Group (TMG) will be responsible for the day-to-day running and management of the trial. Members of the TMG include the chief investigator, coinvestigators, biological coordinators, trial management team leader, senior trial coordinator, trial coordinator, lead trial statistician and trial statistician. The TMG will have regular meetings during recruitment. The TSC will consist of independent clinicians, Dr Bela Wrench and Dr Christina Halsey, as well as an independent statistician, Dr Graham Wheeler.

Data analyses will be supplied in confidence to the independent TSC, which will be asked to support dose decisions and advise on whether the accumulated data from the trial, together with the results from other relevant research, justify the continuing recruitment of further patients. The TSC will operate in accordance with a trial specific charter based on the template created by the Damocles Group. The TSC will meet at the end of every cohort in phase I and at least every 6 months in phase II, or more often if required, for example, an emergency meeting may also be convened if a safety issue is identified. The TSC will report directly to both the SeluDex TMG who will convey the findings of the TSC to the funders/sponsor as appropriate or when specifically requested by these parties.

Confidentiality

Confidential information collected during the trial will be stored in accordance with the relevant data protection legislation in each country, including the General Data Protection Regulation 2018. As specified in the PIS and with the patient's consent, patients will be identified using only their initials, date of birth and unique trial ID number. Authorised staff may have access to the records for quality assurance and audit purposes. The Trials Office maintains the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (eg, laboratory staff).

Trial registration

ISRCTN: 92323261. Date applied: 22 January 2018; date assigned: 23 May 2018. Due to administrative delays, the date assigned occurred 5 days after the first patient was recruited (18 May 2018).

EudraCT: 2016-003904-29. Retrospective registration by UK competent authority (Medicines and Healthcare Products Regulatory Agency, MHRA): 27 March 2019.

ClinicalTrials.Gov: NCT03705507. Retrospective registration: 15 October 2018.
ITCC-063 study

Trial status

Recruitment for the trial opened in April 2018 and the first patient was recruited on 18 May 2018; recruitment is expected to last until 31 January 2023. A list of open sites can be obtained from the SeluDex Trial Office (seludex@trials.bham.ac.uk).

Ethics and dissemination

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland and stated in the respective participating countries laws governing human research, and Good Clinical Practice. The protocol was approved by the medical ethical committees of all the participating countries. UK ethics approval (17/YH/0123) was granted by Yorkshire and The Humber—Leeds West Research Ethics Committee on 12 July 2017. Initial UK Competent Authority approval was granted by the Medicines and Healthcare products Regulatory Agency on 5 May 2017, with subsequent protocol versions approved; current version in use is 9.0, 22 March 2021. Participants are required to provide written informed consent/assent. A meeting will be held after the end of the study to allow discussion of the main results among the collaborators before publication. Results of the primary and secondary endpoints will be disseminated through national and international presentations and submitted for publication in peer-reviewed journals. Manuscripts will be prepared by the TMG and authorship determined by mutual agreement.

DISCUSSION

Position of the trial in an era of CAR-T cell treatment

The SeluDex trial was initially proposed in 2013, before the advent of CAR-T cell and other CD19 and CD22 targeting immunotherapies. This trial was designed for patients who had relapsed after stem cell transplantation, with little or no other therapeutic options. The trial opened in the UK in Spring 2018. Since commercial CAR-T cell treatment (tisagenlecleucel) was approved by the FDA/EMA in 2018, eligible patients were preferentially offered CAR-T cell treatment over enrolment in this experimental study, and this has led to a significant drop in expected trial recruitment. After 2 years of experience with tisagenlecleucel, relapse after cellular immunotherapy is emerging as a new therapeutic challenge.²⁹ Relapses after CAR-T cell failure, especially CD19 negative relapses, and relapsed/refractory T cell ALL should be considered/screened for the SeluDex trial. For patients who have not had CD19 or CD22 targeting immunotherapy these should be prioritised, however, in exceptional circumstances the SeluDex trial (eg, cycle 1)

may also be considered as bridging therapy before CAR-T cell infusion.

Implemented urgent safety measures

Since the study opened to recruitment in 2018 there have been three urgent safety measures (USM) implemented in the protocol to date. The first USM was in December 2018 to reduce the dose of dexamethasone after 2 weeks during cycle 1 for Group A patients, after an adult patient experienced a fatal Suspected Unexpected Adverse Reaction (SUSAR) from rapid onset gram-negative sepsis; investigators suspected that the steroid administration had masked potential symptoms of infection and sepsis. The second USM was implemented in May 2019 to reduce the dose of dexamethasone after 2 weeks during cycle 1 for group P patients, in line with the measure already implemented for adults, in addition to mandating fluoroquinolone prophylaxis during cycle 1 for all patients. This was due to a further fatal SUSAR of gram-negative sepsis in a paediatric patient. The third USM implemented in September 2019 changed the dexamethasone dose to pulsed during cycle 1 and mandated fluoroquinolone prophylaxis in cycle 2, in addition to cycle 1, and co-trimoxazole prophylaxis throughout trial treatment for all patients. This was due to a further fatal SUSAR in an adult patient from pneumonia considered related to trial treatment. Pulsed dosing of dexamethasone (4 days on, 3 days off) is standard practice in the management of adult ALL patients and is better tolerated than continuous dexamethasone dosing during induction. Since these USMs were implemented, there have been no further events of concern and the TMG, TSC and regulatory authorities are confident that the potential patient benefit outweighs the risks of the intervention.

Trial strengths

This trial is, to the best of our knowledge, one of the first to not only use the novel combination of a MEK1/2 inhibitor, selumetinib, with dexamethasone but is also one of the first to span the whole age range of paediatric and adult patients. On the paediatric side, it is only limited because participants need to swallow the selumetinib capsules whole. As soon as a paediatric liquid formulation is available, all age limitations could be removed.

The seamless phase I/II Bayesian trial design with a CRM for dose escalation greatly aids in the delivery of this trial, providing the flexibility to use cohorts of only two patients allowing for more frequent dose adjustment. Additionally, the CRM provides the means to estimate probabilities of DLT at all doses along with associated uncertainty intervals for those estimates, even those untested doses. The CRM in general identifies the MTD with greater accuracy and treats more patients at the MTD than traditional rule-based methods, for example, 3+3.³⁰

Finally, the paediatric part of the SeluDex trial is an approved ITCC in Europe study with five National Co-ordinating Centres (NCC) outside the UK. The NCC of the Netherlands opened in Summer 2020, with

Germany, France, Italy and Denmark planned to follow in 2021/2022. This will help to improve the slow recruitment numbers resulting from the introduction of CAR-T cell therapy.

Summary

In summary, the SeluDex trial investigates the novel combination of the MEK1/2 inhibitor, selumetinib, with dexamethasone in a seamless phase I/II Bayesian trial design, in both adult and paediatric relapsed/refractory ALL patients. Although CAR T-cell therapy was approved after the trial started recruitment, the trial may serve as a bridging treatment option for patients awaiting CAR T-cell therapy and a treatment option for relapses failure once CAR-T cell treatment has failed.

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