PROTOCOL FULL TITLE: Blinatumomab in molecular relapse of AML with a t(8;21) translocation

Protocol Short Title/ Acronym: BlinAML

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Trial Identifiers

EudraCT Number:	2020-002019-23
IRAS Number:	287063

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1. Study Synopsis

Title of clinical trial	Blinatumomab in molecular relapse of AML with a t(8;21) translocation.
Protocol Short Title/Acronym	BlinAML
Trial Phase if not mentioned in title	Phase II
Sponsor name	Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Richard Dillon
EudraCT number	2020-002019-23
IRAS number	287063
Medical condition or disease under investigation	Acute myeloid leukaemia (AML) with a t(8;21) translocation
Purpose of clinical trial	To determine if blinatumomab is a potential alternative to intensive chemotherapy for patients with molecular relapse of AML with a t(8;21) translocation
Primary objective	To evaluate the efficacy of blinatumomab to induce complete molecular remission
Secondary objective (s)	To evaluate: the overall incidence and severity of adverse events, the overall rate of molecular remission, duration of remission, overall survival time and healthcare resource utilization with blinatumomab
Trial design	A single arm phase II Simon's two-stage design for evaluating efficacy of blinatumomab in patients with molecular relapse or molecular persistence of acute myeloid leukaemia (AML) with a t(8;21). All enrolled patients will be statistically evaluated for the primary endpoint of molecular complete response after one cycle of treatment.
Endpoints	Primary – incidence of molecular complete remission after one cycle of treatment. Secondary: • Incidence of patients experiencing a grade 3 or greater non-haematological toxicity during the first cycle of treatment. • Incidence of molecular complete remission at any time from trial entry • Molecular relapse free survival time • Overall survival time • Number of days of hospital admission at 1, 3 and 6 months from entry • Number of days on intravenous antibiotics or antifungals at 1, 3 and 6 months

	• Number of blood components infused at 1, 3 and 6 months.
Sample size	17 patients in total, comprising 7 in Stage I and 10 in Stage II
Summary of eligibility criteria	Confirmed first or subsequent molecular relapse or molecular persistence of AML with t(8;21) following remission induction therapy Documented CD19 expression on blasts at diagnosis or relapse. Adequate bone marrow function Age 18years or older Excluding patients with >5% blasts in BM or evidence of extramedullary relapse. Weight 45kg or greater
IMP, dosage and route of administration	Blinatumomab at 28 mcg/day per day by continuous infusion for 28 days for up to 4 cycles of therapy.
Active comparator product(s)	N/A
Maximum duration of treatment of a participant	4 cycles of 28 days each
Version and date of protocol amendments	

2. Glossary of Terms

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
ALL	Acute lymphoblastic leukaemiae
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
AR	Adverse Reaction
AST	Aspartate transaminase
BiTE	Bispecific T-cell engagers
CA	Competent Authority
CADD	Continuous ambulatory drug delivery
CI	Chief Investigator
CIV	Continuous intravenous
CNS	Central nervous system
CR	Complete remission
CRF	Case Report Form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation Group
CTO	Clinical Trials Office
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEA	European Economic Area
EMR	Electronic medical record
EudraCT	European Clinical Trials Database
FBC	Full blood count
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDAC	High dose cytarabine
HIV	Human immuno-deficiency virus
HSCT	Haematopoietic stem cell transplantation
IB	Investigator Brochure
ICF	Informed Consent Form
IgG	Immunoglobulin G
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional Review Board
ISF	Investigator Site File (This forms part of the TMF)
KHP-CTO	Kings Health Partners Clinical Trials Office
LDH	Lactic dehydrogenase
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRD	Minimal residual disease
NCI	National Cancer Institute
NCRI	National Cancer Research Institute

NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
RSI	Reference Safety Information
RT-qPCR	Real time quantitative polymerase chain reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
sWFI	Sterile water for injection
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
ULN	Upper limit of normal

CONTENTS

3. Background & Rationale

Blinatumomab (AMG103) is a bispecific single-chain antibody construct designed to link B cells and T cells resulting in T-cell activation and a cytotoxic T-cell response against CD19 expressing cells[3-7]. In vitro and in vivo data indicate CD19 positive lymphoma and leukaemia cells to be extremely sensitive to blinatumomab mediated cytotoxicity[3-7]. Blinatumomab has previously been shown to be a highly effective immunotherapeutic approach for patients who have detectable minimal residual disease (MRD) following chemotherapy for B-ALL[12,13], and is approved for this indication[14]. It is well tolerated by ALL patients who are MRD positive but without overt haematological relapse. In the phase II BLAST trial, patients with B-cell ALL in morphological complete remission (CR) with persistent or recurrent MRD positivity received up to four cycles of blinatumomab at a dose of 15 μg/m^2/day for 4 weeks, followed by 2 weeks of no therapy[13]. A total of 116 patients were enrolled, with a median age of 45 years (range, 18–76 years). MRD negativity was achieved in 78% of patients after the first cycle and 88% overall. MRD negativity was associated with a higher overall survival (38.8 *versus* 12.5 months) compared with MRD-positive patients, with a better survival seen for patients treated in first remission. Overall, cytokine release syndrome (CRS) was reported in 3% of patients and neurologic side effects of any grade in 53% of patients, with grade 3 and 4 events in 10% and 3%, respectively. There was a decline in adverse events after subsequent cycles of blinatumomab. A post hoc analysis showed no significant difference in RFS for patients with or without stem cell transplant after blinatumomab, raising the important question of the role of transplant for these patients after they convert to MRD negativity.

With a median follow up of 53.1 months, median OS was 36.5 months, with a plateau after 36 months, suggesting that many of these patients may be cured. Based on these results blinatumomab became the first therapy approved by the US FDA for MRD-positive B-cell ALL in March 2018[14].

The lymphoid marker CD19 is also aberrantly expressed on over 80% of acute myeloid leukaemia patients (AML) with the t(8;21) fusion[8-10], providing a rationale for blinatumomab use in this condition. In a recent report, a patient with a CD19 positive relapsed t(8;21) AML achieved a complete molecular response after blinatumomab therapy[11]. AML with a t(8;21) translocation accounts for approximately 8-10% of cases in younger adults (age <60 years)[15], and is generally regarded as a favourable risk sub-type of AML as there is a cure rate of approximately 60-65% with standard AML chemotherapy[16]. However, relapse still occurs in about one third of patients, requiring further salvage chemotherapy and bone marrow transplantation as a standard of care[1,2]. Some patients may have multiple relapses even post-transplant[16].

The *RUNX1-RUNX1T1* fusion generated by the t(8;21) can be detected and monitored by real time quantitative PCR (RT-qPCR)[17-19] and it is established practice in the UK to undertake regular monitoring of minimal residual disease status using RT-qPCR methodology on bone marrow samples taken following each cycle of induction and consolidation chemotherapy and for two-three years following completion of chemotherapy. Thus, in UK practice relapse or persistence of disease is mainly detected and treated at the molecular level prior to any overt haematological relapse. This gives the possibility of earlier intervention at the level of molecular relapse for patients with rising transcript levels before overt haematological relapse occurs. Earlier intervention may improve response rate and may be better tolerated than salvage treatment at haematological relapse[17,18].

The prognosis for patients with AML who relapse following intensive chemotherapy is generally poor and established treatments are highly suboptimal in terms of efficacy, side effects, cost and quality of life[20]. Allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment but not all patients are able to reach transplant and even for those who do, long-term survival is only 40-50%. For example, in the relapse arm of the NCRI AML17 trial, a second complete remission (CR2) was achieved in 74% of patients but only

57% received a transplant, resulting in 5-year overall survival in the whole cohort of 22%. Reasons for not going to transplant include resistant disease and toxicity of the salvage chemotherapy employed[21].

The standard approach for molecular relapse of AML with t(8;21) is intensive salvage chemotherapy[1,2], a commonly used regimen being FLAG-Ida[21]. The FLAG-Ida salvage chemotherapy regimen is delivered as an in-patient and results in prolonged cytopenias requiring a prolonged in-patient stay (median of 32 days in the NCRI AML17 trial). Critical care admission is required in ~10% of patients. Supportive care requirements are high and patients required a median of 10.4 units of blood, 12.9 units of platelets and 19.3 days of IV antibiotics in the AML17 trial. 60 day mortality in this trial was 6%[21].

For AML with t(8;21) one or two course of salvage chemotherapy is routinely given to patients with molecular persistence or relapse, as these patients will inevitable progress to a full haematological relapse without intervention. MRD monitoring in the UK for both adults and children is provided by the Cancer Genetics Service at Guy's Hospital, London. Samples are analysed and results and clinical advice given in accordance with European LeukaemiaNet guidelines[18].
For patients with molecular relapse, MRD continues to be monitored and is used to track response to salvage chemotherapy and inform timing of transplant and post-transplant intervention. The advantage of this approach is that treatment can be initiated well before a full relapse has occurred when the patient is well and has normal blood counts.

Current treatment for molecular relapse is identical to that for haematological relapse, this is due to the lack of other effective treatment options until now. The development of blinatumomab offers the potential to deliver effective therapy to patients with a molecular relapse and without the need for debilitating intensive in-patient salvage chemotherapy. This approach would offer dramatic improvements in patient experience, quality of life and resource use and provides a potential window of opportunity for outpatient-based therapy.

4. Trial Objectives and Design

4.1. Trial Objectives

In this study we propose to evaluate the safety and efficacy of blinatumomab for up to 4 cycles of therapy in patients with confirmed molecular relapse of t(8;21) positive AML.

The primary objective is to evaluate the efficacy of blinatumomab to induce complete molecular remission (MRD negativity) in patients with molecular relapse or persistence of AML with t(8;21), after one cycle of treatment.

Secondary objectives:

- To evaluate overall survival in patients with molecular relapse or persistence of AML with t(8;21) translocation treated with blinatumomab
- To evaluate the effect of blinatumomab on duration of MRD negativity
- To evaluate the effect of blinatumomab on the kinetics of MRD
- To evaluate resource utilization
- To evaluate the incidence of patients experiencing a grade 3 or greater non-haematological toxicity during the first cycle of treatment.

4.2. Primary endpoints

- Achievement of a molecular complete response defined by absence of detectable *RUNX1-RUNX1T1* fusion transcripts after one cycle of treatment with blinatumomab.

4.3. Secondary endpoints

- Incidence of patients experiencing a grade 3 or greater non-haematological toxicity during the first cycle of treatment.
- Incidence of molecular complete remission at any time from trial entry (evaluated at end of trial)
- Molecular relapse free survival time (evaluated at end of trial)
- Overall survival time (evaluated at end of trial)
- Number of days of hospital admission at 1, 3 and 6 months from entry
- Number of days on intravenous antibiotics or antifungals at 1, 3 and 6 months
- Number of blood components infused at 1, 3 and 6 months

4.4. Trial Design

A single-centre single-arm phase II, Simon's two-stage optimum design study to assess the efficacy of blinatumomab in patients with molecular relapse or molecular persistence of acute myeloid leukaemia (AML) with a t(8;21). Given that the current standard of care is FLAG-Ida, blinatumomab will be considered worth pursuing if it achieves a 75% molecular remission rate; a rate less than 50% would be considered unpromising. Using the recommended design characteristics of 85% power and 15% significance level, 7 evaluable patients will be recruited in stage I. There will need to be at least 4 responses to proceed to stage II, where a further 10 patients will be recruited. Otherwise, the trial will not proceed. If the study proceeds to stage II, and 17 evaluable patients have been recruited, the success criteria are that there are at least 11 responses in total. (Figure 1)

All enrolled patients will be evaluated at each stage for the primary endpoint of molecular complete response after one cycle of treatment, as well as safety and tolerability

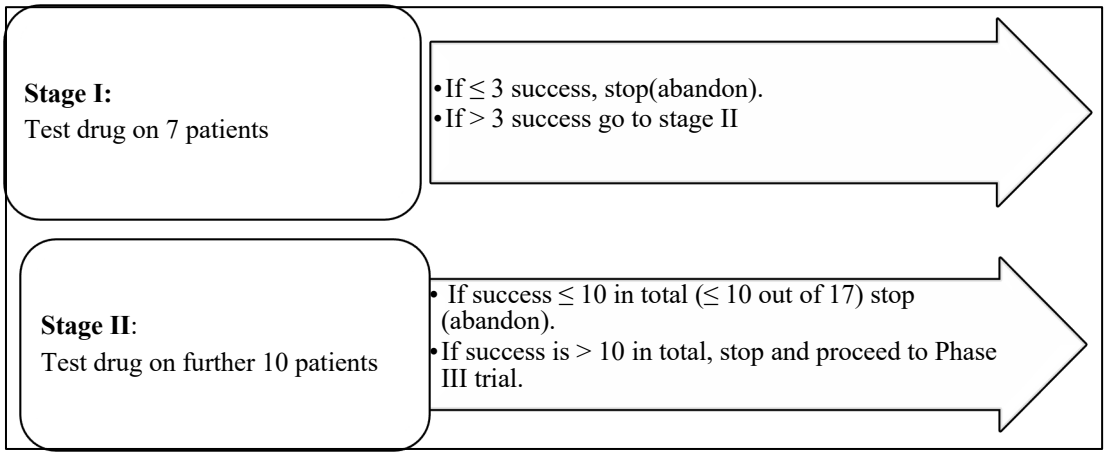

Figure 1 – flowchart of planned patients' recruitment and stopping rules for the study

4.5. Schedule of events

	Screening (within 21 days prior to treatment)	Cycles 1 to 4													90 days after last treatment (+/- 5d)	2-Year Follow-up Period ^	Withdrawal visit
		Day 1*§	Day 2§	Day 3	Day 4	Day 8 (+/- 2d)	Day 11	Day 15 (+/- 2d)	Day 18	Day 22 (+/- 2d)	Day 25	Day 29 (+/- 2d)	Days 30-42 (+ 7d)	Unscheduled visit			
Informed consent	X																
Eligibility assessment	X																
Medical history	X																
Physical exam,vital signs and temperature	X	X	X	X		X		X		X		X		X	X	X	X
Neurological exam and writing test	X	X	X	X		X		X		X		X		X	X		X
ECOG performance status	X															X	
ECG	X														X		X
Urinalysis	X	X	X	X		X		X		X		X			X	X	X
Pregnancy test (if applicable)	X														X		X
Haematology and biochemistry	X	X	X	X		X		X		X		X		X	X	X	X
Virology (HIV, HBV, HCV)	X																
Serum immunoglobulins	X											X			X		X

	Screening (within 21 days prior to treatment)	Cycles 1 to 4												90 days after last treatment (+/- 5d)	2-Year Follow-up Period ^	Withdrawal visit
		Day 1*§	Day 2§	Day 3	Day 4	Day 8 (+/- 2d)	Day 11	Day 15 (+/- 2d)	Day 18	Day 22 (+/- 2d)	Day 25	Day 29 (+/- 2d)	Days 30-42 (+ 7d)	Unscheduled visit			
Bone Marrow aspirate (+/- trephine)	X											X[+]				X	
Response assessment												X					
Blinatumomab infusion		Continuous infusion days 1 – 28 of each cycle										Treatment break					
CADD pump attendance[#]		x			x	x	x	x	x	x	x	x					
Concomitant medications	X	<< Ongoing assessment >>															
Adverse events		<< Ongoing assessment until 90 days after treatment discontinuation >>															X
Supportive Care Requirements		<< Ongoing assessment until treatment discontinuation >>															X

NOTES:

Data on concomitant medications, adverse events and supportive care requirements may be collected during unscheduled visits

§ indicates inpatient visits. All other scheduled visits are outpatient visits.

*Clinical assessments and laboratory assessment performed within 3 days prior to the first dose of blinatumomab will not have to be repeated on day 1 cycle 1

^For patients who did not undergo allogeneic HSCT, Efficacy follow-up visits for assessment of molecular relapse and until haematological relapse will take place 3-monthly (calculated from cycle 1 day 1) within the first year and 6-monthly within the second year until completion of a 2-year period after treatment with blinatumomab. Telephone follow-up will be performed for patients who have undergone HSCT.

[#]Includes initial connection, twice weekly change of infusion bag, and disconnection. To account for weekends and bank holidays, each cycle should start on a Tuesday. Infusion bag changes will therefore occur on Tuesdays and Fridays

[+]In case of technically suboptimal samples, a repeat bone marrow aspiration may need to be performed

5. Trial Medication

5.1. Investigational Medicinal Product

Blinatumomab (AMG103) is a murine recombinant single-chain antibody derivative that combines in one molecule the binding specificity for both the pan-B cell antigen CD19 and the epsilon chain of the T cell receptor/CD3 complex. The molecular weight of blinatumomab is approximately 54 kDa. Blinatumomab belongs to a new series of compounds called bispecific T-cell engagers (BiTE). The antibody is produced by mammalian (Chinese hamster ovarian, CHO) cell suspension culture and purified by affinity and ion exchange chromatography, including viral inactivation and removal procedures.

Blinatumomab is manufactured and will be supplied by Amgen. Information regarding the ordering process, accountability, compliance, returns and destruction will be outlined in the Trial Pharmacy Manual. Delivery lead time is 5 days. Temperature excursions are to be reported to gcte@amgen.com as per the parameters outlined in the Pharmacy Manual.

5.2. Formulation, packaging and labelling

The blinatumomab formulation will be supplied as single-use injection vials containing a white to off-white, lyophilized powder intended for intravenous administration following reconstitution with sterile water for injection (sWFI). Each vial contains a target of 38.5 µg of Blinatumomab and there are 36 vials in a kit.

The formulation will be filled in 4 mL borosilicate clear vials containing the following excipients: citric acid monohydrate, trehalose dihydrate, lysine hydrochloride and polysorbate 80.

The stabiliser solution will be supplied as a 10 mL vial of a clear, colourless-to-slightly-yellow liquid concentrate composed with citrate. The product specific diluent consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride and 0.1% (w/v) polysorbate-80 at pH 7. The information presented on the labels for the IMP will be annex 13 compliant and comply with applicable national and local regulations.

5.3. Storage of IMP

The blinatumomab formulation and the stabiliser solution should both be stored between 2°C and 8°C in their original outer package within a secure environment, protected from light and separated from other medication or investigational products. Do not freeze. Blinatumomab concentrate does not contain any preservatives. The reconstitution has to be done in controlled and validated aseptic conditions. Parenteral products should be inspected visually for particulate matters and discoloration beyond a pale yellow colour (due to the administration of the stabiliser solution) prior to administration. If these are present, blinatumomab final solution must not be used and the Sponsor should be informed immediately. Please refer to the Investigator's Brochure for further details, particularly for current data concerning the stability of blinatumomab. If shelf-life of the product will be extended during the trial supported by corresponding stability data, relabelling of study medication at the pharmacies is possible, but must follow detailed instructions provided in the Pharmacy File.

5.4. Preparation

The final blinatumomab solution for infusion should be prepared in a clean, sterile environment using aseptic techniques at the study site's pharmacy, even if the patient is treated as an outpatient. The volume (dose) of blinatumomab is calculated based on the patient's weight. As all patients will be greater than 45kg,the dose is 28 mcg/day.

Blinatumomab lyophilized powder for solution, the stabiliser solution and the final solution for infusion are for single use only. Any remaining concentrate or final solution for infusion should be disposed of.

First, the lyophilized formulation of blinatumomab will be reconstituted with 3 mL sterile water for injection (sWFI). Then, it will be further diluted into a 0.9% sodium chloride solution (normal saline) intended for intravenous infusion in 250 mL infusion bags. The used water for injection and sodium chloride solution must be commercially available and marketed in the United Kingdom for the purpose of intravenous infusion, marked with the exact Pharmacopeia term. Since blinatumomab will be administered via continuous intravenous route, it needs to be stabilized at low concentrations and must be prevented from adsorbing to surfaces. Therefore, the normal saline bag must be conditioned by prior addition of a product-specific diluent (stabiliser solution), resulting in a final diluent concentration of 0.5 mM citrate, 25 mM lysine hydrochloride and 0.002% (w/v) polysorbate80. Detailed instructions regarding the reconstitution and dilution of blinatumomab as well as the preparation of the IV bag prior to administration will be provided to the respective pharmacy before the investigational product will be applied for the first time (refer to Pharmacy Manual).

Blinatumomab will be administered via a continuous ambulatory drug delivery (CADD) pump. Blinatumomab solution for infusion must be administered at ambient temperature and must not be kept at ambient temperature more than 96 hours.
For storage prior to administration, the prepared infusion solution must be kept at 2°C to 8°C. The total storage and administration time must not exceed 10 days

5.5. Dosing Regimen

Patients will receive one to four consecutive cycles of blinatumomab. A cycle consists of a continuous intravenous infusion at a dose of 28 mcg/day over four weeks followed by an infusion free interval of two weeks. Patients will receive four cycles of treatment, unless criteria for treatment discontinuation apply. The duration of one cycle is 6 weeks, including a four week continuous intravenous infusion and a two week infusion free interval, which may be extended by a maximum of 7 days. In case of haematological relapse, the study treatment will be permanently discontinued. Patients are generally are expected to receive four cycles of treatment, independently from achieving complete molecular response. If patients are suitable for allogeneic HSCT after treatment with at least one treatment cycle of blinatumomab, they may undergo allogeneic HSCT instead of receiving further cycles with blinatumomab. Following the last treatment cycle, there will be a safety follow-up visit at 90 days after last infusion, documented as End-of-Core-Study Visit, followed by efficacy follow-up visits at three, six, nine, 12, 18 and 24 months after treatment start. Efficacy follow-up visits at six months will only be applicable for patients completing less than 4 cycles, at three months only for patients having completed 1 cycle only.

After completion of the two year efficacy follow-up period, information concerning haematological relapse free, leukaemia treatment free and overall survival as well as further data on hospitalisation and the use of relevant anti-leukemic, antibiotic, and antifungal medication and transfusion of blood products, and hospitalisation, if available, will be gathered by telephone at least every six months until death or at least until five years after treatment start, whichever occurs earlier. Patients who discontinue treatment prematurely

will enter immediately the efficacy and/or survival follow-up study. Patients who discontinue treatment before completion of the first treatment cycle will be assessed for MRD response on day 29 (and day 43, if applicable) of cycle 1 before entering the efficacy and/or survival follow-up study. In case of haematological relapse within the treatment period, treatment will be terminated at the time of relapse.

5.6. Administration

Blinatumomab will be administered as a continuous intravenous (CIV) infusion at a constant flow rate rate as specified on the prescription, via a low protein binding infusion line with 0.2 micron inline filter using a CADD Ambulatory Infusion Pump. The infusion is for four weeks followed by a two-week infusion free interval, which may be prolonged for up to seven more days, if deemed necessary. There should be no planned interruptions in the infusion, e.g. for i.v. administration of other medication. Patients will be hospitalized during at least the first three days after start of infusion of the first treatment cycle and during at least the first two days after start of infusion of subsequent cycles. After interruption of treatment for more than 4 hours, the infusion should be restarted in the hospital, under supervision of the investigator. After interruptions for up to 4 hours, the infusion can be continued without specific measures.

The CADD infusion bags will be prepared as either 72 hour or 96 hour infusions, with the bags being changed twice a week. To account for weekends and bank holidays, this will occur on Tuesdays and Fridays. Each cycle should being on a Tuesday.

The infusion rate of the 250mL bag depends on the duration of the infusion:

- 72 hour infusions: Administer at a constant infusion rate of 3.33 mL/h over 72 hours, to achieve a final infusion volume of 240 mL for each subject. Any remaining infusion solution volume present in the infusion lines must be discarded.
- 96 hour infusions: Administer at a constant infusion rate of 2.5 mL/h over 96 hours, to achieve a final infusion volume of 240 mL for each subject. Any remaining infusion solution volume present in the infusion lines must be discarded.

Problems with the infusion bag, pump, or intravenous access should be rectified as soon as possible by contacting the Acute Oncology Service on 020 7188 3754

5.7. Treatment Interruptions/Dose modification for toxicity

For all patients consideration to discontinue blinatumomab temporarily or permanently as appropriate should be made in the case of the following severe (grade 3) or life-threatening (grade 4) toxicities: cytokine release syndrome, tumour lysis syndrome, neurological toxicity, elevated liver enzymes and any other clinically relevant toxicities. If the interruption of treatment after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle. If the toxicity takes more than 14 days to resolve, discontinue therapy permanently.

5.8. IMP Risks

In case of any clinical/laboratory adverse event considered being medically relevant treatment may be interrupted or permanently discontinued at the discretion of the investigator. All treatment interruptions except for regular infusion bag changes will be documented clearly and concisely in the electronic medical record before being recorded with electronic Case Report Forms. Infusion bag changes, however, need to be documented in the patient's file.

Expectedness of SAEs is based on the Reference Safety Information listed in Appendix B of the Blinatumomab Investigators Brochure 2019.

Further information on the management of adverse events, including instructions on interruption of blinatumomab and supportive care, is included in the Appendix.

5.9. Criteria for Treatment Discontinuation

Treatment with blinatumomab will be discontinued in the event of any of the following:

- Haematological or extramedullary relapse
- Confirmed molecular progression between cycles (>1 log rise)
- Investigator's decision that a change of therapy is in the patient's best interest
- Patient or investigator not compliant with the study protocol
- Progression of a medical condition which in the opinion of the investigator should lead to treatment discontinuation
- Administration of relevant non-permitted concomitant medication(s)
- Occurrence of an adverse event which makes discontinuation from treatment desirable or necessary in the investigator's and/or the patient's opinion
- Infusion interruption of more than two weeks due to AE
- Central laboratory determination that the patient's screening bone marrow demonstrates that the patient was ineligible for study treatment due to MRD negativity at the time of enrolment.
- Occurrence of toxicities as described in the Appendix

5.10. Patient Monitoring

The patient is to be an in-patient during the first two days of each treatment cycle (three days of the first cycle) because of potential side effects associated with T cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses and physicians trained in management of medical emergencies should be available for immediate intervention in case of complications.

5.11. Out-patient Treatment

Blinatumomab will be administered on an in-patient basis during at least the first three days after start of infusion of the first treatment cycle and during at least the first two days after start of infusion of each following cycle or if necessary for restart of treatment following temporary discontinuations due to adverse events. Afterwards the treatment will be continued on an out-patient basis, if it seems to be safe and feasible to the investigator. For the approval of an out-patient treatment the following conditions will have to be met:

- The patient will be able and willing to visit the investigator at the study centre according to the study visit schedule, which is weekly during the infusion period assuring infusion bag change, monitoring of vital signs, and monitoring/documentation of AE/SAE.
- In addition, regular visits to the study site infusion centre by the patient for review by a well-trained nurse or medical doctor being thoroughly familiar with the study will be guaranteed assuring infusion bag change, maintenance of port, and, monitoring of vital signs.
- A continuous ambulatory drug delivery (CADD) pump will monitor delivery of the IMP.

5.12. Management of overdose

Overdoses have been observed including one patient who received 133-fold the recommended therapeutic dose delivered over a short duration. Overdoses resulted in adverse reactions which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, the infusion should be temporarily interrupted and patients should be monitored. Re-initiation of blinatumomab at the correct therapeutic dose should be considered when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion. Overdose, with or without any signs or symptoms, will be handled and reported as a serious adverse event (SAE).

5.13. Premedication

The clinical experience with blinatumomab has resulted in implementation of a premedication regimen described below:

Obligatory Pre-Medication:

- In adult patients, dexamethasone 20 mg intravenous should be administered 1 hour prior to initiation of each cycle of blinatumomab.
- Anti-pyretic use (e.g. paracetamol) is recommended to reduce pyrexia during the first 48 hours of each treatment cycle

During the treatment period:

In case of CNS-related events dexamethasone should be administered orally at a dose of at least 24 mg per day for up to three days. The dose will then be step-wise reduced over up to four days. If the CNS event was a seizure, appropriate prophylactic anticonvulsant treatment with a therapeutic dose of e.g. phenytoin or levetiracetam will be administered during restart and during start of the following new treatment cycle. For further information see Appendix.

5.14. Concomitant Medication

The following medication and therapies will be prohibited during the study until end of the efficacy period:

- Any anti-tumour therapy other than the investigational product i.e. cytotoxic and/or cytostatic drugs, radiation therapy or immunotherapy.
- Any other investigational agent
- Chronic systemic high-dose corticosteroid therapy (i. e. > 20 mg prednisone daily)
- Any other immunosuppressive therapies (except for protocol mandated interventional corticosteroids)
- Non-steroidal anti-inflammatory drugs (NSAIDs, except for paracetamol and naproxen)
- Tyrosine kinase inhibitors

For management of concomitant therapies, please refer to the Investigators Brochure. A complete listing of all concomitant medication received during the treatment phase must be recorded in the relevant CRF. This will include all medications at baseline and any changes during the treatment period.

6. Selection and Withdrawal of Participants

6.1. Inclusion Criteria

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to

the Trial Manager before randomisation/registration and no eligibility wavers will be permitted.

1) Patients with AML with a t(8:21) translocation in complete haematological remission (defined as less than 5% blasts in bone marrow) with a confirmed first or subsequent molecular relapse or molecular persistence of disease (defined according to European Leukaemia Net criteria) following remission induction therapy comprising 2 courses of an anthracycline based regimen or one course of an anthracycline based regimen plus a second course of high dose cytarabine (HDAC).
2) Bone marrow or peripheral blood specimen from primary AML sample taken at diagnosis documented as showing expression of CD19.
3) Bone marrow function as defined below:
   - Neutrophils >1x10^9/L - Platelets > 20 x 10^{12}/L (transfusion permitted)
   - Haemoglobin level >9g/dl (transfusion permitted)
4) Renal and hepatic function as defined below:
   - AST , ALT , and ALP < 2 x upper limit of normal (ULN) - Total bilirubin < 1.5 x ULN
   - Creatinine clearance >50 mL/min (calculated according Cockroft & Gault)
5) Negative HIV antibody test, negative hepatitis B (HbsAg) and hepatitis C virus (anti-HCV) test with the exception of well controlled chronic infections with at least two documented undetected PCR tests for viral load.
6) Negative highly sensitive pregnancy test in women of childbearing
7) ECOG Performance Status 0 – 2.
8) Age 18 years or older
9) Ability to understand and willingness to provide written informed consent.

6.2. Exclusion Criteria

1) 5% or more blasts in the bone marrow or the presence of circulating blasts or current extramedullary involvement by AML.
2) History of relevant CNS pathology or current relevant CNS pathology (e.g. seizure, paresis, aphasia, cerebrovascular ischemia/haemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder).
3) Current infiltration of cerebrospinal fluid by AML.
4) Body weight under 45kg
5) History of or active relevant autoimmune disease.
6) Prior allogeneic HSCT within the last 3 months prior to study treatment.
7) Systemic cancer chemotherapy within 2 weeks prior to study treatment.
8) Radiotherapy within 4 weeks prior to study treatment.
9) Treatment with any investigational product within four weeks prior to study treatment.
10) Previous treatment with blinatumomab.
11) Known hypersensitivity to immunoglobulins or to any other component of the study drug formulation.
12) History of malignancy other than AML within five years prior to treatment start with blinatumomab, with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix.

13) Active infection, any other concurrent disease or medical condition that are deemed to interfere with the conduct of the study as judged by the investigator.

14) Nursing women or those with a positive pregnancy test

15) Women of childbearing potential (as defined in CTFG guidelines, see appendix) not willing to use a highly effective form of contraception (as defined in CTFG guidelines) during participation in the study and for at least 3 months thereafter, or male patients not willing to ensure use of highly effective contraception during participation in the study and for at least three months thereafter.

16) Patients currently enrolled in another interventional clinical trial

6.3. Selection of Participants

Participants will be identified by their direct care team (most commonly their treating haematologist) at the hospital which they receive their care. If a participant is interested in taking part in the study, they will be referred to the trial investigators. In some circumstances the trial investigators may also be the direct care team for a patient.

6.4. Consent

The Chief Investigator or delegated clinician will inform the patient of all aspects pertaining to their participation in the study and that participation in the study is voluntary and that they can withdraw at any time. The patient's free and expressed informed consent will be obtained in writing prior to the screening procedures required for entry into the study according to all applicable regulatory requirements. The written Informed Consent Form must be dated and signed by both the investigator (or his designee) and the patient before any study related procedure will be initiated.

A copy of the signed consent form will be given to every subject, the original will be retained in the investigator site file and a copy will be filed in the patient's medical notes.

6.5. Screening logs

A screening log of all patients who were either ineligible or eligible but not consented will be so that any biases from differential recruitment will be detected.

Subject numbers will be allocated on Castor EDC.

6.6. Withdrawal of Participants

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial. Withdrawn patients will be replaced to ensure that the study maintains sufficient statistical power.

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data/samples collected prior to participant withdrawal unless the patient requests that either the data or the samples or both are destroyed. Otherwise, the use of the data and samples collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a participant wishes to stop taking part in the trial completely, they will need attend a withdrawal visit. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you will need to continue to collect information about them for as long as the reaction lasts.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial medication
- Withdrawal of consent for treatment by the participant
- Any alteration in the participants condition which justifies the discontinuation of the treatment in the Investigator's opinion
- Non-compliance

In all instances participants who consent and subsequently withdraw should complete a withdrawal form or this should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant.

6.7. Expected Duration of Trial

The trial is expected to take 3 years to complete. The end of trial will be defined as the time of database lock.

6.8. Site and Investigator selection

This trial will be carried out at a single participating site during the first stage and up to two additional sites may be added by amendment for the second stage, depending on speed of enrolment

7. Trial Procedures

7.1. Screening

7.1.1. Eligibility Screening Period

Written informed consent must be obtained from each patient at or prior to the start of the 21-day screening period and before performance of any study-specific procedure. Standard of care MRD samples may be analysed prior to screening or enrolment onto this clinical trial.

All patients who have signed the Informed Consent Form (ICF) will be recorded on the Subject Screening Log. The patient is considered as being enrolled onto the study once written informed consent has been obtained. The eligibility screening period starts with the first study specific assessment after the ICF has been signed by the patient. Each patient will be assigned a unique patient identification number. If a patient is screened but not treated, the reason should be recorded. That patient's number will not be re-used.

Clinical assessments and laboratory assessment performed within 3 days prior to the first dose of blinatumomab will not have to be repeated on day 1 cycle 1. All results will be available before a patient will be declared eligible for study participation.

7.1.2. Eligibility Assessments

The following procedures and assessments must be performed during the screening period within three weeks prior to the first administration of the investigational product (Day 1):

<u>Inclusion/Exclusion</u>

Assessment of the patient's eligibility will be performed as outlined in section 6, including review of all laboratory measurements performed during the screening period. Eligibility will also need to be confirmed at treatment initiation.

Demographics

Date of birth, sex and ethnic origin will be recorded at screening.

Medical History/Current Medical Conditions

General and disease specific medical history including a history of past and current medical conditions, full history of the course of the patient's leukaemia including immunophenotype, karyotype, molecular phenotype, data on disease subset specifics, information on prior anti-tumour therapies and current eligibility for HSCT will be recorded at screening.

Physical Examination

Comprehensive physical examinations of all body systems will be performed at the screening visit.

Neurological Examination

During the screening visit a neurological examination will be performed including the test of the following functions: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extrapyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (e.g., speech, cognition and emotion).

Writing Test

Patients will be asked to perform a writing test at screeningt in order to monitor patients for the onset and resolution of writing difficulties which may be an indicator for neurological AEs.

ECOG Performance Status

The patient's performance status will be assessed at screening using the Eastern Cooperative Oncology Group (ECOG) score.

Vital Signs

Body temperature, heart rate and blood pressure (systolic/diastolic) will be measured during screening

Electrocardiogram (ECG)

Standard 12-lead ECG will be performed at screening.

Blood tests

Blood samples for laboratory evaluations will be taken at screening. The following analyses will be performed:

- Serum chemistry
- Glucose, sodium, urea, uric acid, potassium, calcium, magnesium, phosphate, chloride, creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), total serum protein, albumin, lactic dehydrogenase (LDH), C-reactive protein (CRP).
- Full blood count
- Coagulation screen
- Serum immunoglobulins (IgG)
- Creatinine clearance (e.g., determined by Cockroft and Gault) will be performed during the screening period to detect any severe kidney function impairment.

- Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) antibody and Human Immuno-deficiency Virus (HIV) testing will be performed during the screening period to exclude an untreated active infection with the respective viruses.

Urinalysis

The presence of glucose, protein and blood in urine will be assessed by dipstick during screening, at D1 prior to the start of infusion at each cycle, and at the End-of-Study visits.

Hepatitis B/C and HIV Testing

Pregnancy Test

A pregnancy test (β-human chorionic gonadotropin [β-HCG] in urine or serum) will be performed at screening in all women of childbearing potential. If at any time during the conduct of the study, a pregnancy is suspected, a pregnancy test should be performed immediately. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible and must be discontinued from study treatment immediately.

Bone marrow biopsy

A bone marrow aspirate, and trephine if necessary, will be performed during the screening period. Patients are potentially eligible for enrolment based on results of RT-qPCR assessment of the screening bone marrow aspirate and one of the following criteria must be fulfilled:

- Two consecutive positive samples with an increase in *RUNX1-RUNX1T1* transcript expression of more than 1 $\log_{10}$ in a patient who previously tested negative in at least two technically adequate samples (molecular relapse)
- Two consecutive positive samples with an increase in *RUNX1-RUNX1T1* transcript expression of more than 1 $\log_{10}$ in a patient who previously tested positive below a level of 500 copies / 10^5 ABL (molecular progression)
- Two consecutive samples which both test positive at a level above 500 copies / 10^5 ABL after the completion of primary therapy (molecular persistence of disease).

Concomitant Medication

All concomitant medications will be recorded starting at the first day of screening

7.2. Treatment Period (Cycle 1 - 4)

Patients will be hospitalised during at least the first three days of the first cycle and during at least the first two days of each following cycle. Before starting the infusion of blinatumomab, the patient will be examined physically and blood samples for safety laboratory parameters will be taken. For starting the study treatment the laboratory results will not have to be awaited.

Following the start of the infusion AE/SAE and concomitant medication will be evaluated continuously throughout the whole study until the 90-day visit. After the 90-day visit, only (S)AEs potentially related to blinatumomab should be documented in the CRF (and reported to the sponsor, if applicable). In addition, only anti-leukemic concomitant medication and medication related to blinatumomab related (serious) adverse events should be documented in the CRF. The vital signs and the laboratory tests will be repeated on D2 and D3 and at each visit during the treatment period.

Replacement of infusion bags will be performed as described in the Operations Manual. CADD pump infusion bags will be changed twice a week. To account for weekends and bank holidays, this will be on Tuesdays and Fridays. Each treatment cycle should begin on a Tuesday.

7.2.1. Treatment Period (Day 1 - Day 29 of each treatment cycle)

Prior to Infusion (D1)

- Physical examination
- Vital signs/temperature – it is recommended to monitor the patient's vital signs continuously every four hours during the first 24 hours after start of treatment/dose step.
- Neurological examination and writing test
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC (aproximately 30mL of blood)
- Urinalysis
- Concomitant medication
- AE/SAE assessment
- CADD pump attachment

During Infusion (D2 to D22)

The following procedures and tests will be performed on D1 to D29 during blinatumomab infusion:

- Physical examination (D2, D3, D8, D15, D22)
- Vital signs/temperature (D2, D3, D8, D15, D22). On D2 and D3 vital signs should be measured at least twice a day
- Neurological examination and writing test (D2, D3, D8, D15, D22)
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC (D2, D3, D8, D15, D22) (aproximately 30mL of blood)
- Concomitant medication ()
- AE/SAE assessment ()
- CADD pump change on days 4, 8, 11, 15, 22 and 25

At the end of the infusion period of cycle two to four the procedures and tests of D29 of the first cycle will be repeated.

End of Infusion (D29)

The following procedures and tests will be performed on D29 (end of infusion):

- Physical examination
- Vital signs/temperature
- Neurological examination and writing test
- Bone marrow aspiration/biopsy
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC (aproximately 30mL of blood)
- Serum Immunoglobulins (IgG)
- Concomitant medication
- AE/SAE assessment

Infusion free Interval from Day 30 to Day 43 (applies to each treatment cycle)

After completion of the 4-week infusion period a 2-week infusion-free period will follow before a new cycle starts. During this time, the patient will not need to visit the study centre. The infusion free interval may be prolonged for up to seven more days, if deemed necessary. If the treatment will be continued, study day 43 of the previous cycle will be day 1 of the subsequent cycle.

7.2.2. D43/D1 of Subsequent Cycle

If the treatment will be continued with a further cycle, the patient will be hospitalised for two days and the following procedures and tests will be performed:

- Physical examination
- ECOG performance status
- Neurological examination and writing test
- Vital signs/temperature
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC (aproximately 30mL of blood)
- Urinalysis
- Concomitant medication
- AE/SAE assessment
- Confirmatory bone marrow aspiration in case of central MRD result shows that the previous sample was technically inadequate.

7.3. Follow-up Period

7.3.1. 90-day Safety Follow-up Visit

A Safety follow-up visit will be performed at 90 days after the end of infusion with blinatumomab. In case an allogeneic HSCT is planned following treatment with blinatumomab, the 90-day Safety Follow-Up Visit should be performed at the latest possible timepoint prior to the initiation of transplant conditioning, even if the 90 days have not elapsed. This visit will also be documented as End-of-Core-Study Visit and the following procedures and tests will be performed:

- Physical examination and ECOG performance status
- Neurological examination
- Writing test
- Vital signs/temperature
- 12-lead ECG
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC (aproximately 30mL of blood)
- Urinalysis
- Pregnancy test (in women of childbearing potential)
- Serum immunoglobulins (IgG)
- Concomitant medication
- AE/SAE assessment

7.3.2. 2-Year Efficacy Follow-up Period

For patients who did not undergo allogeneic HSCT, Efficacy follow-up visits for assessment of molecular relapse and until haematological relapse will take place 3-monthly (calculated from cycle 1 day 1) within the first year and 6-monthly within the second year until completion of a 2-year period after treatment with blinatumomab. The following procedures and tests will be performed:

- Physical examination and ECOG performance status
- Vital Signs/Temperature
- Bone marrow aspirate/biopsy
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC (aproximately 30mL of blood)
- Urinalysis
- Recording of anti-leukemic concomitant medication
- Recording of AE possibly related to blinatumomab

For patients who underwent allogeneic HSCT the investigator will contact the patients or his/her treating physician (e.g. via phone) to receive information concerning haematological relapse free and overall survival. Also, information concerning the conditioning regimen, donor type and 100d HSCT related mortality will be collected in the CRF. In addition to the routine collection of adverse events within the core study and until 90 days after last administration of study medication, investigators will report adverse events possibly related to blinatumomab thereafter.

7.4. Unscheduled Visits

Unscheduled visits should be performed whenever necessary, i.e. in case of adverse events or in case of symptoms of clinical disease progression. Evaluations and/or assessments will be performed, as deemed appropriate by the investigator based on the nature of the event. Results will be documented in the patient's file and recorded in the CRF. If a patient is withdrawn from the study, efforts should be taken to perform all examinations scheduled for the End-of-Core-Study visit (please see section 7.5.1, 30-day Safety Follow-up Visit).

7.5. In Case of Adverse Events

The following procedures and assessments will be performed in the case of an unscheduled visit resulting from an adverse event:

- Physical examination
- Vital signs/temperature
- Routine bloods, U/E, LFTs, LDH, Coagulations screen, FBC

In case of neurological adverse events leading to treatment interruption/discontinuation or dose reduction, the following additional assessments should be performed:

- Cranial MRI
- Assessment of cerebrospinal fluid, if appropriate

7.6. Laboratory procedures

All laboratory samples collected, including urine, blood and bone marrow, will be processed using routine standard of care procedures. All assessments are performed at Guy's Hospital with no requirement for shipment or analysis at other institutions.

All blood and bone marrow samples collected would be considered standard of care for a patient being treated for AML. These samples will be used for research purposes in the study.

8. Assessment of Efficacy

8.1. Definitions for Treatment Response Evaluation

- Complete molecular response is achieved if there is no amplification of *RUNX1-RUNX1T1* fusion transcripts in a technically adequate sample obtained after the first cycle of treatment.
- Two weeks after the first post treatment bone marrow sample was obtained (which is expected to be identical with day 1 of the second cycle), another bone marrow aspiration has to be obtained in case the previous specimen was technically suboptimal and did not allow evaluation for molecular complete response.
- Molecular relapse is defined as re-appearance of *RUNX1-RUNX1T1* fusion transcripts on two consecutive samples with an increase in transcript expression of

more than 1 log_{10} in a patient who previously tested negative in at least two technically adequate samples
- Molecular progression is defined as an increase in disease-related transcript expression levels of more than 1 log_{10} confirmed on a second consecutive sample.
- Haematological relapse is defined as unequivocal detection of > 5% leukaemia cells in bone marrow as measured by cytological, microscopic assessment, presence of circulating leukaemia blasts, or extramedullary leukaemia.

8.2. Procedures for Assessing Efficacy Parameters

RT-qPCR analysis on the bone marrow aspirate performed on day 29 of cycle 1 will be used to assess the primary endpoint. Verification of receipt of a sufficient sample by the central MRD lab is a rate limiting step for determination of eligibility and potential protocol treatment.

Procedures for assessment of secondary endpoints will include

- Regular and unscheduled clinical assessments for AEs/SAEs as outlined in section 7
- RT-qPCR on bone marrow aspirates performed at the end of each treatment cycle
- Follow-up assessments (refer to section 7.3) to assess for relapse and survival
- Review of CRFs and patient medical notes to assess days of hospital admission, antibiotic and antifungal use and blood component transfusions

8.3. Bone Marrow Aspiration

Evaluation of MRD will be performed on bone marrow aspirate samples. Each bone marrow will be evaluated for presence of leukaemia cells with differential count by light microscopy at the local laboratory and results entered on the CRF.

At the end of the first treatment cycle (D29) a bone marrow aspiration will be performed and shipped to the central MRD laboratory for the evaluation of the primary endpoint. In case of technically suboptimal samples (i.e. *ABL* Ct >26), a second bone marrow aspiration will be performed to confirm whether the primary endpoint of complete molecular response was reached or not.

At the end of each treatment cycle (D29) and during the efficacy follow-up visits a bone marrow aspiration will be performed to evaluate MRD and morphology defining the percentage of leukemic blasts in bone marrow. Furthermore, in the event of abnormal blood counts (suggesting leukemic relapse), a bone marrow evaluation should be performed prior to initiating the subsequent cycle of treatment with blinatumomab.

Additional tests conducted by the investigators but not required by protocol such as immuno-phenotypic, cytogenetic or molecular analyses during the study will be collected and documented in the CRF. During the study, haematological/morphological assessments of the bone marrow will be performed locally.

9. Assessment of Safety

Adverse events (AEs) will be reported from the time of consent up to ninety days after the completion of the final dose of Blinatumomab.

All serious adverse events (SAEs) must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the Clinical Trials Office (CTO).

9.1. Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a clinical trial participant administered a medicinal product, which is not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.2. Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements above, for the purposes of this trial the following events will also be considered SAEs: Complications at the central venous catheter site like infections, thrombosis or leakage are commonly observed complications in the treatment of leukaemia patients and are to be expected in this trial. An identified complication that involves the central venous catheter, even though it does not meet the definition of a SAE is to be reported on a SAE Report Form and will be processed as a SAE. Such a device-related complication must be documented and reported to Amgen as event related to study procedure.

Life-threatening and fatal adverse reactions are considered unexpected for the purpose of expedited reporting.

9.3. Causality

Causal relationship will be assessed for blinatumomab (IMP) only.

The Chief Investigator (or another delegated medically qualified doctor from the trial team) will assess each SAE to determine the causal relationship:

Relationship	Description	Reasonable possibility that the SAE may have been caused by the IMP?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

9.4. Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for blinatumomab. Expectedness decisions must be based purely on the content of the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease.

SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the RSI is considered unexpected.

9.5. Reporting procedures

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE report to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own trust in accordance with local practice.

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO and CI for review in accordance with the current Pharmacovigilance Policy.

The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the KHP-CTO and Amgen may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

jcto.pharmacovigilance@kcl.ac.uk

Adverse events should be reported from the time of signature of informed consent, throughout the treatment period up to, and including 90 days after the participant receives their last dose of the IMP. Serious adverse reactions (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow up.

Adverse events (AE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The toxicity grades should be recorded on the toxicity part of the CRF.

9.6. SUSAR reporting

Guy's and St Thomas' Hospitals NHS Trust is undertaking the duties of trial Sponsor and has delegated to the Kings Health Partners Clinical Trials Office (KHP-CTO) the responsibility for reporting SUSARs and other SARs to the regulatory authorities (MHRA and relevant ethics committees) and to Amgen as follows:

The KHP-CTO will report SUSARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at theKHP- CTO. If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report.
- SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the KHP-CTO. Any additional, relevant information must be reported within a further 15 days.
- SUSARs will be reported to the Amgen Safety department at the same time as reporting to the MHRA and REC.

9.7. Safety reports

The Chief Investigator and KHP-CTO on behalf of the sponsor, will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA, REC, Amgen annually.

The Trial Manager will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

9.8. Contraception and pregnancy

Pregnancy

There are no data from the use of blinatumomab in pregnant women. Blinatumomab should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

Women of childbearing potential who are sexually active with a non-sterilised male partner, and non-sterilised male patients with a partner of childbearing potential, must use at least one form of effective contraception during and for at least 3 months after treatment with blinatumomab.

A woman is considered of childbearing potential following menarche and until becoming post-menopausal unless:

- Permanently sterile – has undergone hysterectomy, bilateral salpingectomy or bilateral oophorectomy.
- Post-menopausal state - no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.Highly effective forms of contraception are defined as: combined hormonal contraception or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, a vasectomised partner, or sexual abstinence.

In case of exposure during pregnancy, depletion of B-cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B-cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B-cell count has recovered.

All pregnancy exposures will be reported to Amgen Safety department within 15 days (within one day if there is concern about potential harm to a pregnant woman or foetus).

Breast-feeding

It is unknown whether blinatumomab or metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast-feeding is contraindicated during and for at least 48 hours after treatment with blinatumomab.

All potential lactation exposures will be reported to Amgen Safety department within 15 days (within one day if there is concern about potential harm to a nursing mother or infant).

Fertility

No studies have been conducted to evaluate the effects of blinatumomab on fertility. No adverse effects on male or female mouse reproductive organs in 13 week toxicity studies with the murine surrogate molecule

9.8.1. Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in the trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Information on a pregnancy in a trial participant will be captured on the SAE Report Form. Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTO. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTO within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

9.9. Premature Termination of the Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring & Ethics Committee.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

10. Statistics

The study will use a Simon's two-stage design to assess the efficacy of blinatumomab in patients with molecular relapse or molecular persistence of acute myeloid leukaemia (AML) with a t(8;21). This type of AML has a relatively good prognosis. The study primarily wants to establish activity and early efficacy from the first cycle of blinatumomab. The first group of patients will be recruited at stage I, and if the success criteria are met, the study will proceed to stage II where the second group will be recruited. Safety will be assessed in terms of grade 3+ toxicity, and excessive toxicity will be monitored and assessed regularly through follow-up visit that will be performed at 90 days after the end of infusion with blinatumomab.

10.1. Sample Size

A single-arm phase II, Simon's two-stage design study (1) with primary endpoint, the incidence of molecular complete remission after one cycle of treatment in patients with molecular relapse or molecular persistence of acute myeloid leukaemia (AML) with a t(8;21) after course 1. Given that the current standard of care is FLAG-Ida, blinatumomab will be considered worth pursuing in a head-to-head comparison if it achieves a 75% molecular remission rate; a rate less than 50% would be considered unpromising. Using the recommended design characteristics of 85% power and 15% significance level, 7 evaluable patients will be recruited in stage I. There will need to be at least 4 responds to proceed to stage II, where a further 10 patients will be recruited. Otherwise, it is not. After the study proceed to stage II, and 17 evaluable patients have been recruited, the success criteria are that there are at least 11 responds in total. (Figure 1)

All enrolled patients will be statistically evaluated for the primary endpoint of molecular complete response after one cycle of treatment. The study aims to test the null hypothesis that P ≤ P0 (where P is the true proportion responding to blinatumomab treatment versus the alternative hypothesis that P ≥ P1). Where, P0 = the largest response proportion which, if true, clearly implies that blinatumomab treatment does not warrant further study, P0=50%; P1 is the smallest response proportion which, if true, clearly implies that blinatumomab treatment does warrant further study, P1=75%.Using α=15%, as the probability of rejecting the null hypothesis when it is true & β=15% being the probability of rejecting the alternative hypothesis when it is true.

All enrolled patients will be statistically evaluated for the secondary endpoints of safety and tolerability

10.2. Analysis

All patients who have received at least one dose of the trial treatment will be included in the per-protocol analysis. The primary endpoint will be described in numerical terms and as a percentage of all participants. An interim analysis will be performed after 7 patients have been treated, as outlined in section 10.1. Final analysis will be performed at the completion of the trial.

As there are no between-group comparison planned, significance testing is not required. Survival end-points will be assessed at the end of the study, and calculated using the Kaplan-Meier method. AEs and SAEs will be reported as incidences for each patient and each cycle of treatment. The best response attained by each participant throughout the trial will be used to determine the molecular complete remission rate.

There will be no data imputation for missing data in the primary endpoints. Deviations from the initial statistical plan will be described and justified in the report of the trial results.

11. Trial Management Group

Further details of the TMG will be provided in the next version of the protocol.

12. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. participants' case sheets, blood test reports, X-ray reports, histology reports etc.).

13. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to EudraCT on behalf of the Sponsor

14. Quality Assurance

14.1. Monitoring

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI & PI

14.2. Audits and Inspections

The trial is participant to inspection by MHRA as the regulatory body. The trial may also be participant to inspection and audit by Guy's and St Thomas' NHS Trust under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

The site will inform the KHP-CTO of any MHRA inspections.

15. Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Participant data will be pseudo-anonymised.
- All pseudo-anonymised data will be stored on a secure online data management system.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

16. Data Management

Source data for this trial will comprise the patients electronic medical record (EMR), electronic case report forms (eCRF) and the molecular data held within the trial laboratory. All data are to be stored and transmitted securely in accordance with the General Data Protection Regulation 2016. Data will be managed by the Chief Investigator and aspects of data collection and management may be delegated to nominated deputies including research nurses and clinical research fellows.

17. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

18. Insurance / Indemnity

Non-negligent harm: This trial is an academic, investigator-led and designed trial. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any

indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Guy's and St Thomas' NHS Trust does not accept liability for any breach in other hospital's duty of care, or any negligence on the part of employees of other hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

18.1. Trial sponsorship

Guy's and St Thomas' NHS Foundation Trust will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial. The Trust shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996).
- Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005).
- The General Data Protection Regulation 2016.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

18.2. Funding

This study is funded by an Educational Grant awarded by Amgen to Guy's and St Thomas' NHS Foundation Trust.

19. Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Sponsors Archiving Standard Operating Procedure (SOP). The research data and Trial Masterfile will be archived using the IRON Mountain archiving service for 5 years.Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and relevant SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

_____	_____
Chief Investigator	Date

20. REFERENCES

1. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129:424-47.
2. O'Donnell MR, Tallman MS, Abboud CN, et al. Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2017;15:926-57.
3. Bargou R, Leo E, Zugmaier G, et al. Tumor regression in cancer patients by very low doses of a T cell-engaging antibody. Science 2008;321:974-7.
4. Loffler A, Kufer P, Lutterbuse R, et al. A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. Blood 2000;95:2098-103.
5. Loffler A, Gruen M, Wuchter C, et al. Efficient elimination of chronic lymphocytic leukaemia B cells by autologous T cells with a bispecific anti-CD19/anti-CD3 single-chain antibody construct. Leukemia 2003;17:900-9.
6. Dreier T, Lorenczewski G, Brandl C, et al. Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody. Int J Cancer 2002;100:690-7.
7. Schlereth B, Quadt C, Dreier T, et al. T-cell activation and B-cell depletion in chimpanzees treated with a bispecific anti-CD19/anti-CD3 single-chain antibody construct. Cancer Immunol Immunother 2006;55:503-14.
8. Kita K, Nakase K, Miwa H, et al. Phenotypical characteristics of acute myelocytic leukemia associated with the t(8;21)(q22;q22) chromosomal abnormality: frequent expression of immature B-cell antigen CD19 together with stem cell antigen CD34. Blood 1992;80:470-7.
9. Tiacci E, Pileri S, Orleth A, et al. PAX5 expression in acute leukemias: higher B-lineage specificity than CD79a and selective association with t(8;21)-acute myelogenous leukemia. Cancer Res 2004;64:7399-404.
10. Walter K, Cockerill PN, Barlow R, et al. Aberrant expression of CD19 in AML with t(8;21) involves a poised chromatin structure and PAX5. Oncogene 2010;29:2927-37.
11. Plesa A, Labussiere-Wallet H, Hayette S, Salles G, Thomas X, Sujobert P. Efficiency of blinatumomab in a t(8;21) acute myeloid leukemia expressing CD19. Haematologica 2019;104:e487-e8.
12. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol 2011;29:2493-8.
13. Gokbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131:1522-31.
14. Curran E, Stock W. Taking a "BiTE out of ALL": blinatumomab approval for MRD-positive ALL. Blood 2019;133:1715-9.
15. Grimwade D, Ivey A, Huntly BJ. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. Blood 2016;127:29-41.
16. Christen F, Hoyer K, Yoshida K, et al. Genomic landscape and clonal evolution of acute myeloid leukemia with t(8;21): an international study on 331 patients. Blood 2019;133:1140-51.
17. Rucker FG, Agrawal M, Corbacioglu A, et al. Measurable residual disease monitoring in acute myeloid leukemia with t(8;21)(q22;q22.1): results from the AML Study Group. Blood 2019;134:1608-18.
18. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood 2018;131:1275-91.

19. Gabert J, Beillard E, van der Velden VH, et al. Standardization and quality control studies of 'real-time' quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia - a Europe Against Cancer program. Leukemia 2003;17:2318-57.
20. Burnett AK, Goldstone A, Hills RK, et al. Curability of patients with acute myeloid leukemia who did not undergo transplantation in first remission. J Clin Oncol 2013;31:1293-301.
21. Burnett AK, Hills RK, Nielsen OJ, et al. A comparison of FLAG-Ida and daunorubicin combined with clofarabine in high-risk acute myeloid leukaemia: data from the UK NCRI AML17 Trial. Leukemia 2018;32:2693-7.

21. APPENDICES

- Common Terminology Criteria for Adverse Events (NCI CTC) v5
- WHO / ECOG Performance Status
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- SmPC and data sheet for blinatumomab
- Pharmacy information manual
- Methods for collecting participant samples, their storage and dispatch and handling conditions
- Declaration of Helsinki (1996 version)
- Clinical Trials Facilitation Group Recommendations related to contraception and pregnancy testing in clinical trials
- Management of adverse events

21.1. Management of adverse events

Toxicity	Grade*	Blinatumomab action	Other actions
Cytokine release syndrome, tumour lysis syndrome	Grade 3	Interrupt blinatumomab Once resolved restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days
	Grade 4	Discontinue blinatumomab permanently.	Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days
Neurological toxicity	Convulsion	Discontinue blinatumomab permanently if more than one convulsion occurs.	Prophylactic anticonvulsant treatment with a therapeutic dose of, for example, phenytoin or levetiracetam during restart and during start of the following new treatment cycle
	Grade 3	Interrupt blinatumomab until no more than grade 1 (mild) and for at least 3 days Restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.	For reinitiation, premedicate with a 24 mg dose of dexamethasone. Then reduce dexamethasone step-wise over 4 days Re-start of the infusion should take place in hospital, and the patient monitored as an inpatient for at least 2 days.
	Grade 4	Discontinue blinatumomab permanently.	
Elevated liver enzyme Other clinically relevant (as determined by treating physician) adverse reactions	Grade 3	If clinically relevant, interrupt blinatumomab until no more than grade 1 (mild) Restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	
	Grade 4	Consider discontinuing blinatumomab permanently.	

*Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Grade 1 to 2 adverse events should be managed with observation and symptomatic therapies.

For all interruptions due to adverse events:

- If the toxicity takes more than 14 days to resolve, discontinue permanently
- Discontinue therapy permanently if there is reappearance of the same grade 3 or 4 events
- If the interruption of treatment after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.