Safety and efficacy of post-haematopoietic cell transplantation maintenance therapy with blinatumomab for relapsed/refractory CD19-positive B-cell acute lymphoblastic leukaemia: protocol for a phase I–II, multicentre, non-blinded, non-controlled trial (JPLSG SCT-ALL-BLIN21)

Hirotoshi Sakaguchi,1 Katsustugu Umeda,2 Itaru Kato,2 Kimiyoshi Sakaguchi,1,3 Hidefumi Hiramatsu,2 Hiroyuki Ishida,4 Hiromasa Yabe,5 Hiroaki Goto,6 Yuta Kawahara,7 Yuka Iijima Yamashita,8 Masashi Sanada,8 Takao Deguchi,1 Yoshiyuki Takahashi,9 Akiko Saito,8 Hisashi Noma1,10 Keizo Horibe,8 Takashi Taga,11 Souichi Adachi,12 On behalf of Transplantation and Cellular Therapy Committee of Japanese Childhood Cancer Group

ABSTRACT
Introduction Relapsed and refractory B-cell acute lymphoblastic leukaemia (R/R-B-ALL) is linked to a significant relapse rate after allogeneic haematopoietic cell transplantation (allo-HCT) in children, adolescents and young adults (CAYA). No standard treatment has been established to prevent relapse after allo-HCT for R/R-B-ALL, which is an unmet medical need. The administration of blinatumomab after allo-HCT is expected to enhance the antileukaemic effect on residual CD19-positive blasts by donor-derived CD3-positive T-cells.

Methods and analysis The goal of this multicentre, open-label, uncontrolled, phase I–II clinical trial is to assess the safety and effectiveness of post-transplant maintenance therapy with blinatumomab for CAYA patients (25 years old or younger) with CD19-positive R/R-B-ALL who have received allo-HCT beyond first complete remission (CR) and have CR with haematological recovery between 30 and 100 days after allo-HCT. Eighty-five paediatric institutions in Japan are participating in this study. Forty-one patients will enrol within 2.25-year enrolment period and follow-up period is 1 year. The primary endpoints are the treatment completion rate for phase I study and the 1-year graft-versus-host disease-free/relapse-free survival rate for phase II study, respectively.

Ethics and dissemination This research was approved by the Central Review Board at National Hospital Organization Nagoya Medical Center (Nagoya, Japan) on 21 January 2022 and was registered at the Japan Registry of Clinical Trials (jRCT) on 3 March 2022. Written informed consent is obtained from all patients and/or their guardians. The results of this study will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number JRCTs041210154.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This study is anticipated to establish evidence for post-transplant maintenance therapy with blinatumomab for childhood, adolescent and young adult patients with CD19-positive relapsed and refractory B-cell acute lymphoblastic leukaemia.
⇒ The study is designed as a Japanese nationwide, multicentre, non-blinded, non-controlled, phase I–II trial.
⇒ Immuno-monitoring, minimal residual disease-monitoring and microbiome analysis performed in this study are expected to identify novel biomarkers for transplant outcomes.
⇒ The study will not provide information on long-term complications or prognosis beyond 1 year.

INTRODUCTION
The long-term survival rate of B-cell acute lymphoblastic leukaemia (B-ALL) in children, adolescents and young adults (CAYA),
with an incidence of 600–700 cases per year in Japan, has reached 80%–90% due to the improvement of supportive care as well as optimisation of treatment intensity through risk stratification using National Cancer Institute (NCI)/Rome criteria (age and white cell count at diagnosis), cytogenetic aberrations and minimal residual disease (MRD).\(^1\) Alternatively, relapsed/refractory (R/R) B-ALL, frequently induction failure or early relapse, is frequently resistant to chemotherapy, and the prognosis is poor with a high relapse rate after allogeneic haematopoietic cell transplantation (allo-HCT).\(^2\)\(^3\) Furthermore, the long-term survival rate of patients who underwent a second allo-HCT for relapse after the first allo-HCT is approximately 20\%.\(^4\) As a result, prevention of post-transplant relapse is critical to enhancing the prognosis in patients with R/R-B-ALL. Although immunological interventions, such as the early discontinuation of immunosuppressive agents and donor lymphocyte infusion, have been used to treat post-transplant relapse, they have not been accepted as standard treatments due to their low response rate and high risk of developing graft-versus-host disease (GvHD).\(^5\)\(^6\) To date, post-transplant treatment with tyrosine kinase inhibitors has been widely used as an efficient maintenance treatment for Philadelphia chromosome (Ph) positive ALL,\(^7\) whereas there is no proven post-transplant maintenance therapy for Ph negative ALL. A medical need that has yet to be met is the establishment of a maintenance therapy after allo-HCT for R/R-B-ALL.

Blinatumomab is a CD3/CD19-directed bispecific T-cell engager molecule that engages CD3-positive T cells to remove CD19-positive cells, resulting in an antileukaemic effect for a subset of B-cell malignancies.\(^8\) For CD19-positive R/R-B-ALL, blinatumomab treatment has been shown to achieve a higher remission induction rate than conventional chemotherapy.\(^9\)\(^10\) Moreover, blinatumomab has been shown to be safer and more helpful than standard chemotherapy as intensification therapy after remission induction therapy and bridge therapy to allo-HCT for patients with R/R-B-ALL.\(^11\)\(^12\) Regarding post-transplant administration of blinatumomab, 29 of 64 patients with R/R-B-ALL who created haematological relapse after allo-HCT achieved complete remission (CR) by blinatumomab therapy; however, approximately 80% of patients later relapsed within 1 year.\(^13\) As a result, early blinatumomab administration for patients who maintain haematological CR after allo-HCT is expected to enhance the antileukaemic effect of engrafted donor-derived CD3-positive T cells on minimal residual CD19-positive leukaemia cells, resulting in lower relapse rates and increased survival in R/R-B-ALL patients at high risk of post-transplant relapse. However, there are worries about the development and exacerbation of GvHD and other complications with post-transplant maintenance therapy with blinatumomab, which should be investigated in clinical trials.

Gabella et al recently reported in a single-centre phase II study the feasibility of four-cycle blinatumomab maintenance therapy with 3-month intervals for adult patients with CD19-positive R/R-B-ALL in haematological CR during the first year after allo-HCT. They showed that blinatumomab maintenance therapy following transplant is feasible with a very safe toxicity profile. Furthermore, they stated that the response to blinatumomab therapy is affected by immune status such as proportions of effector memory CD8 T-cell subsets.\(^14\)

The present protocol is for a multicentre, non-blinded, non-controlled, phase I–II trial, JPLSG SCT-ALL-BLIN21 (protocol version 1.1, released on 23 December 2021), sponsored by Japanese Children’s Cancer Group (JCCG; http://jcgg.jp/), to assess the safety and effectiveness of post-transplant maintenance therapy with blinatumomab for CD19-positive R/R-B-ALL in CAYA.

**METHODS AND ANALYSIS**

**Aim and study design**

This study is a multicentre, non-blinded, non-controlled, phase I–II trial. The goal of this study is to evaluate the safety and effectiveness of post-HCT maintenance therapy by blinatumomab for relapsed/refractory CD19 positive R/R-B-ALL.

**Endpoints**

**Primary endpoint**

Phase I

- Study treatment completion rate.

Phase II

- GvHD-free, relapse-free survival (GRFS) rate at 1 year after transplantation.

An event is defined as grades 3–4 acute GvHD, moderate/severe chronic GvHD, relapse, secondary cancer (including myelodysplastic syndrome) and death. GRFS is estimated from the date of allo-HCT to the date of identification of any of the above-listed events. GvHD and secondary cancer are recorded as events that occurred on the date that the diagnosis was confirmed. Patients with no events have their data censored at the end of the follow-up period.

**Secondary endpoints**

Phase I

1. Percentage of NCI-Common Terminology Criteria (NCI-CTCAE) V.5.0 grade 3 or higher adverse events within each course.

Phase II

1. Cumulative incidence of GvHD at 1 year after transplantation.

2. Cumulative incidence of secondary graft failure (GF) at 1 year after transplantation.

3. Cumulative incidence of relapse at 1 year after transplantation.

4. Cumulative incidence of non-relapse mortality (NRM) at 1 year after transplantation.
5. Disease-free survival (DFS) rate at 1 year after transplantation.
6. Overall survival (OS) rate at 1 year after transplantation.
7. Occurrence of NCI-CTCAE V.5.0 grade 3 or higher adverse events within each course.

**Eligibility criteria**

**Inclusion criteria**
1. Patients with CD19 positive precursor B-ALL who were under the age of 25 at the time of enrolment.
2. Eastern Cooperative Oncology Group-Performance Status 2 or less.
3. Clinical stage at the time of receiving allo-HCT.
   - Phase 1, non-remission, third or more CR.
   - Phase 2, beyond the first CR.
4. At the time of registration, patients must have attained a neutrophil count of 0.5×10^9/L or higher without 48 hours of granulocyte colony-stimulating factor administration and a platelet count of 20×10^9/L or higher without 72 hours of platelet transfusion at least 30 days but less than 100 days after transplantation.
5. A bone marrow test performed at the time of enrolment confirmed haematological remission.
6. Written informed consent obtained from patient or guardians.

**Exclusion criteria**
1. Other than blinatumomab, antileukaemic agents are administered after allo-HCT to treat the primary disease.
2. At the time of enrolment, active grades 2–4 acute GvHD or moderate-to-severe chronic GvHD and administration of immunosuppressive drugs (including systemic steroids) for the treatment of GvHD. Immunosuppressive agents may be administered to prevent GvHD. Acute grade 1 GvHD can be treated with topical steroids).
3. Presence of lesions in the central nervous system at the time of enrolment.
4. Less than 20% of blasts assessed diagnosis or relapse had CD19 expression.
5. Four or more consecutive courses of blinatumomab up to just before the start of the pretransplant conditioning regimen.
6. History of enrolment in this study following a previous transplantation.
7. Active infection at the time of enrolment.
8. At the time of enrolment, patients have any of the following: hepatic impairment (aspartate aminotransferase/alanine aminotransferase>5×upper limit of normal [ULN], T:Bil>2.5×ULN), renal impairment (Cre>2×ULN), respiratory impairment requiring oxygenation, heart failure with ejection fraction <40% or neurological disease with frequent seizures.
9. HIV antibody positive, HBs antigen-positive or hepatitis C virus antibody positive.
10. Women who are pregnant or are planning to become pregnant.
11. If the principal investigator or subinvestigator judges that participation in this study is not appropriate.

**Central review for diagnosis and treatment evaluation**
- Immuno-monitoring: National Center for Child and Development (flow cytometry (FCM)) and Kyoto University (mass cytometry).
- MRD monitoring: National Center for Child Health and Development (FCM), National Hospital Organization Nagoya Medical Center (quantitative PCR) and Nagoya University (next-generation sequencing).
- Microbiome analysis: Jichi Medical University (metagenomic analysis).
- Chimerism analysis: HLA laboratory (short-tandem repeat-PCR).

**Treatment procedures**

This study consists of two courses of blinatumomab therapy administered as a continuous intravenous infusion over 4 weeks with 2 weeks intervals. Dosage and administration are determined following the standard guidelines for R/R-B-ALL patients in children and adults.

**Course-1**

Patients ≥45 kg received 9 µg of blinatumomab daily administered as a continuous infusion on days 1–7, then 28 µg/day as a continuous infusion on days 8–28; and patients <45 kg received 5 µg/m^2/day (maximum: 9 µg/day) as a continuous infusion on days 1–7, then 15 µg/m^2/day (maximum: 28 µg/day) as a continuous infusion on days 8–28, respectively.

**Course-2**

Patients ≥45 kg received 28 µg of blinatumomab daily administered as a continuous infusion on days 1–28, and patients <15 kg (dose based on body surface area) received 15 µg/m^2/day (maximum: 28 µg/day) as a continuous infusion on days 1–28.

In accordance with the drug information for blinatumomab, administration should be interrupted or discontinued according to each adverse event. The handling of this study treatment after interruption or discontinuation shall be governed by the following provisions.

(1) When the first course is interrupted.
- If the interruption period is 7 days or less, the same course should be administered for 28 days including the interruption period.
- If the interruption period is between 8 and 14 days, the first course is terminated and the second course proceeds.
- If the interruption period exceeds 15 days, the study treatment is discontinued.

(2) When the first course is discontinued.
- The study treatment is discontinued.

(3) When the second course is interrupted.
The study treatment consists of two courses of blinatumomab (BLIN) therapy administered as a continuous intravenous infusion over 4 weeks with a 2-week interval. At each time point (TP with asterisk symbol), central testing will be conducted, including chimerism, minimal residual disease, immunophenotype and microbiome tests. Clinical outcomes for patients will then be reported 1 year after enrolment.

- If the interruption period is 7 days or less, the same course should be administered for 28 days including the interruption period.
- If the interruption period exceeds 8 days, the study treatment is discontinued.
- (4) When the second course is discontinued.
- The study treatment is discontinued.
- Until the leukaemia relapses, none of the following treatments should be administered during the study period:
  - Another HCT.
  - Other molecular targeted agents (inotuzumab ozogamicin, tyrosine kinase inhibitor, etc) and anti-cancer agents (exception: rituximab for Epstein-Barr virus-associated B-cell lymphoproliferation is acceptable).
  - Additional irradiation.
  - Donor lymphocyte infusion.
  - CD19-directed chimeric antigen receptor T cell therapy.

The treatment scheme for the study is shown in figure 1.

### Follow-up and study status

Follow-up will be performed every month for the first year after the completion of the study treatment. If necessary, additional tests will be performed in addition to clinical examinations. We will collect information associated with blinatumomab 1 year after allo-HCT. Patient enrolment began in March 2022 and is scheduled to end in June 2024, and that study data collection will be ongoing until June 2025.

### Data management

All data relevant to the trial, including patient’s characteristics, treatment doses, adverse events, discontinuation or deviation of treatment, clinical outcomes and central laboratory results, will be collected by the Electronic Data Capture system. An independent data centre fixes the data after cleaning and passes the data set to the investigators.

### Sample size considerations

Based on the results of the preliminary analysis (as shown in figure 2), the expected value in this study considered as 60% because of the risk of an increased incidence of GvHD while a decreased recurrence rate is expected with post-transplant BLIN administration. Supposing a one-sided test with a threshold of 40%, the minimum sample size needed to accomplish a significance level of 5% and a power of 80% was 39 cases (test of one-sample survival probability based on the Kaplan-Meier method). Considering a drop-out rate of 5%, the sample size was set at 41 cases. In this study, the enrolment period will be 2.25 years, followed by a 1-year observation period, for a total of 3.25 years.

### Statistical analysis

#### Phase I

Enrolment will be halted when the first sixth patient is enrolled, and the completion rate of the study treatment (two courses of blinatumomab) will be evaluated in the six patients in phase I. Patients whose completion of study treatment is reported through the electronic data capture system will be defined as treatment completion, and the percentage of patients who complete treatment will be measured.

- Enrolment in the phase II study will be restarted if the completion rate is four out of six or higher.
- If the completion rate is three out of six cases, another three cases will be added to phase I. If two or more of the additional three cases are complete, the phase II study will be restarted. This study will be terminated if only one or lesser of the remaining three cases is completed.
- This study will be terminated when two or fewer patients out of six completed the study treatment.

#### Phase II

The full analysis set includes all registered patients, including patients who enrolled in phase I, who fulfil the eligibility criteria and receive at least one cycle of blinatumomab and is used as the efficacy and safety analysis population in phase II. The GRFS rate at 1 year after HCT will be estimated using the Kaplan-Meier method for primary analysis in this study. GRFS events are defined as grades 3–4 acute GvHD, moderate-to-severe chronic
GvHD, disease relapse or death from any cause during the first 12 months after allo-HCT.\textsuperscript{15} The cumulative incidences of GvHD, secondary GF, relapse and NRM, as well as the probabilities of DFS and OS and percentages of NCI-CTCAE V.5.0 grade 3 or higher adverse events, will be described in secondary analysis, along with their 95\% CIs. OS is defined as the time interval from allo-HCT to death from any cause. DFS is defined as the duration of survival in continuous CR after allo-HCT. A clinical and haematological recurrence of leukaemia was defined as relapse. Death from any cause other than relapse was defined as NRM. The probabilities of GvHD, secondary GF, relapse and NRM will be estimated using cumulative incidence curves; secondary GF, secondary malignancy, relapse and death without relapse will be competing risks for GvHD; secondary malignancy, relapse and death without relapse will be competing risks for secondary GF; secondary GF, secondary malignancy and death without relapse will be competing risks for relapse; and secondary GF, secondary malignancy and relapse will be competing risks for NRM. All data will be considered as censored at the end of follow-up period. To estimate the SE of the survival rate at a specific time point, the Greenwood formula will be used when there is no competing risk, and the counting process method will be used when there is competing risk, respectively. Unless otherwise stated, statistical tests are two sided, the \( \alpha \) levels are set at 0.05, and the confidence coefficients for the confidence intervals are set at 95\%. For exploratory assessment, subgroup analysis stratified to patients/transplants’ characteristics and biomarkers examined by the central lab will be performed. The log-rank test and Gray test will be used for the tests of survival curves and cumulative incidence curves, respectively. As an exploratory endpoint, prognostic factors will be investigated to evaluate the relationship of prognosis with novel molecular cytological markers and post-transplant immune profiles. The HR and CI for survival rates will be estimated using the Cox’s regression, and those for cumulative incidences will be estimated using Fine-Gray model.

**Monitoring**

To confirm whether the study is carried out safely according to its protocol and whether accurate data are gathered, regular monitoring is performed once a year in all registered patients primarily based on case reports. Central monitoring is conducted based on the data reported using case reports collected at a data centre.

**Participating institutions**

Eighty-five institutions are participating as of 1 March 2022 (online supplemental table). Most of the major paediatric oncology centres in Japan participate in this trial, which is responsible for patient recruitment, study treatment, follow-up and input into the EDC. Important protocol modifications will be disseminated to each institution via the Secretariat’s mailing list.

---

**Figure 2** Results of preliminary analysis. Preliminary analysis using the database of the Japanese Data Center for Hematopoietic Cell Transplantation revealed that the 1 year graft-versus-host disease (GvHD)/relapse-free survival (GRFS) rates of the children/adolescent and young adult patients (under 25 years old at the time of transplantation) who received allogeneic hematopoietic cell transplantation for B-cell acute lymphoblastic leukaemia beyond first complete remission (CR1) between 2008 and 2017, and survived without GvHD and relapse until 30, 50, 60, 80 and 99 days after transplantation) were 44.2\%, 49.1\%, 51.2\%, 54.9\% and 60.6\%, respectively.
ETHICS AND DISSEMINATION

This research was approved by the Central Review Board at National Hospital Organization Nagoya Medical Center (Nagoya, Japan) on 21 January 2022 and was registered at the Japan Registry of Clinical Trials (jRCT) on 3 March 2022 (jRCTs041210154). WHO trial registration data set can be found at https://jRCT.niph.go.jp/en-latest-detail/jRCTs041210154. Written informed consent is obtained from all patients or their guardians. An example of the participant consent form can be available in online supplemental material. The results of this study will be disseminated through peer-reviewed publications and conference presentations.

Author affiliations
1Children’s Cancer Center, National Center for Child Health and Development, Tokyo, Japan
2Department of Pediatrics, Graduate School of Medicine, Kyoto University, Kyoto, Japan
3Department of Pediatrics, Hamamatsu University School of Medicine, Hamamatsu, Japan
4Department of Pediatrics, Kyorin University School of Medicine, Tokyo, Japan
5Department of Pediatric Hematology/Oncology, Kanagawa Children’s Medical Center, Yokohama, Japan
6Department of Pediatrics, Jichi Medical University School of Medicine, Tochigi, Japan
7Clinical Research Center, National Hospital Organization Nagoya Medical Center, Nagoya, Japan
8Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan
9Department of Data Science, The Institute of Statistical Mathematics, Tokyo, Japan
10Department of Pediatrics, National Hospital Organization Isehara Medical Center, Isehara, Japan
11Department of Pediatrics, Shiga University of Medical Science, Otsu, Japan
12Department of Pediatrics, Graduate School of Medicine, Kyoto University, Kyoto, Japan
13Children’s Cancer Center, National Center for Child Health and Development, Tokyo, Japan
14Clinical Research Center, National Hospital Organization Nagoya Medical Center, Nagoya, Japan
15Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan
16Department of Data Science, The Institute of Statistical Mathematics, Tokyo, Japan
17Department of Pediatrics, Shiga University of Medical Science, Otsu, Japan
18Human Health Science, Kyoto University, Kyoto, Japan

Acknowledgements The authors thank all the JCCG investigators involved in the JPLSG SCT-ALL-BLIN21 trial, especially to following; Risa Watanabe and Wakana Kakegawa from the JPLSG data center for support of protocol creation and managing the study; and Asako Sugimura from the Department of Cancer Genomics of the National Center for Child Health and Development for administrative support as secretariat. We also appreciate the Japanese Data Center for Hematopoietic Cell Transplantation (Director, Professor Yoshiko Atsuta) providing the data for the preliminary analysis.

Contributors HS (principal investigator), KU (chair of Transplantation and Cellular Therapy Committee of the Japanese Childhood Cancer Group); IK, KS, HH, HI, HY, HS and YT wrote the manuscript; HS and KU performed statistical analysis; HS and KU conceived and designed the study; and all authors are contributing to the conduct of the trial and provided final approval of the manuscript.

Funding This study was supported by grants for Practical Research for Innovative Cancer Control from the Japan Agency for Medical Research and Development (AMED; JP22ck0106678h0002).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Hiroshi Sakaguchi http://orcid.org/0000-0003-0236-1187
Kimiyoshi Sakaguchi http://orcid.org/0000-0002-3665-401X
Hisashi Noma http://orcid.org/0000-0002-2520-9949

REFERENCES