Summary Table of Study Protocol

Title	Expanded access of Blincyto® in patients with acute lymphoblastic leukaemia: a retrospective observational study (Neuf Study)
Protocol version identifier	**Superceding Amendment 1**
Date of last version of the protocol	**6th November** 2017
EU Post Authorisation Study (PAS) Register No	Not available
Active Substance	Blinatumomab
Medicinal Product	Blincyto
Product Reference	H0003731
Procedure Number	NA
Marketing Authorisation Holder(s)	Amgen Europe B.V. Minervum 7061 4817 ZK Breda The Netherlands
Joint PASS	No
Research Question and Objectives	The primary objective is to describe the clinical characteristics and treatment patterns of patients with B precursor acute lymphoblastic leukemia, having received Blincyto® in the expanded access setting and identify clinically relevant subgroups
Countries of Study	France, Spain, Italy, United Kingdom, Russia
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Marketing Authorisation Holder

Marketing authorisation holder(s)	**Amgen Europe B.V.** Minervum 7061 4817 ZK Breda The Netherlands
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Investigator's Agreement

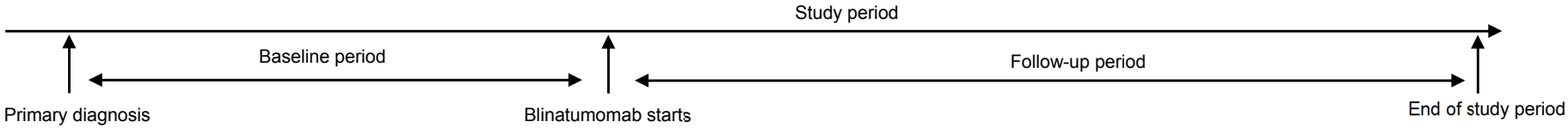
I have read the attached protocol entitled "Expanded access of Blincyto® in patients with acute lymphoblastic leukaemia: a retrospective observational study (Neuf Study)", dated **20th November 2017**, and agree to abide by all provisions set forth therein.

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema

This is a retrospective chart review study in which data will be collected from patient records to conduct the analysis depicted by the below schema



Baseline Period

Clinical and treatment characteristics:

- Demographics
- Medullary and extramedullary involvement
- Immunophenotype
- Cytogenetics/molecular biology
- Prior chemotherapy
- Prior HSCT
- Treatment response
- MRD results
- Mutation history
- Disease status
- Comorbidities

Follow-up Period

Effectiveness:

- CR
- CR/CRh
- CR/CRh/CRi
- RFS, EFS, DFS, OS
- Allogeneic HSCT, GvHD, graft failure
- MRD response
- 100-day mortality after HSCT
- Subsequent immunotherapy/chemotherapy
- CD19 haematological relapse

Blincyto Utilisation:

- Duration of treatment
- Number cycles initiated
- Dosing schedule
- Reasons for interruptions/reductions
- Dexamethasone use
- Reasons for discontinuation
- Hospitalisation
- Outpatient visits
- Concurrent ALL therapies

CR = complete response; CRh* = complete response with partial recovery of peripheral blood counts; CRi = complete response with incomplete recovery of peripheral blood counts; HSCT = haematopoeitic stem cell transplantation; RFS = relapse-free survival; OS = overall survival; EFS = event-free survival; DFS = disease-free survival; MRD = minimal residual disease;

3. Responsible Parties

Sponsor	Amgen Limited 1 Uxbridge Business Park Sanderson Rd Uxbridge UB8 1DH
Study Coordinating Centre	OXON Epidemiology Ltd Doctor Fleming 51 28036 Madrid, Spain
Principal Investigator:	PPD Hopital Saint Louis 1 Avenue Claude Vellefaux, 75010, Paris, France

4. Abstract

- Study Title

Expanded access of Blincyto® in patients with acute lymphoblastic leukaemia: a retrospective observational study (Neuf Study)

- Study Background and Rationale

Blincyto® (blinatumomab) was approved by the Food and Drug Administration (FDA) in December 2014 and was conditionally approved in November 2015 by the European Medicine's Agency for the treatment for adults with relapsed and/or refractory (R/R) Philadelphia chromosome-negative (Ph-) B-precursor acute lymphblastic leukaemia (ALL). Additionally, in August 2016 the FDA also approved the use of Blinctyo in paediatric patients. The clinical development program also consists of clinical trials to assess Blincyto in additional ALL populations : paediatric R/R and first relapse ALL; patients with minimal residual disease; and Ph+ patients R/R to tyrosine kinase inhibitors (TKI).

Due to the high level of unmet clinical need in this patient population, Amgen has been providing Blincyto via an early access program for a number of ALL subgroups who met pre-specified disease criteria in countries where such programs were permitted. Additionally country-level expanded access programs were set up to facilitate access to patients, e.g. Temporary Authorisation for Use (ATU) in France.

This study will aim to characterise the ALL patient population and the specific subgroups receiving Blincyto in the expanded access setting and describe selected outcomes and Blincyto utilisation.

- Research Question and Objectives

Primary Objective

- To describe the clinical characteristics and treatment patterns of patients with B precursor ALL, having received Blincyto in the expanded access setting and identify clinically relevant subgroups

Secondary Objectives

- To describe the effectiveness of Blincyto within identified subgroups as outlined in Section 9.6.2.5
- To describe Blincyto utilization within identified subgroups as outlined in Section 9.6.2.5

Hypothesis/Estimation

- This study is descriptive and no formal hypothesis will be tested.

- Study Design/Type

This is a retrospective, observational, multi-centre study involving medical record review of patients who initiated Blincyto that was provided via an expanded access program.

- Study Population

This study is planned to be conducted in **five** countries: France, , Italy, Spain, UK and Russia. Eligible patients will include ALL patients who have initiated Blincyto in the expanded access setting from 1st January 2014 up until **30th June 2017**.

- Summary of Patient Eligibility Criteria

Inclusion:

- B-precursor ALL patients who have initiated Blincyto in an expanded access setting from 1st January 2014 up until **30th June 2017**

Exclusion:

- Patients enrolled in Amgen expanded access protocol 20130320
- Patients who do not provide informed consent, where required per country regulations
- Patient's medical chart is not available for data extraction

- Follow-up

For the purposes of analysis, the follow-up period is defined as the period from the start of Blincyto initiation in the expanded access setting until death, entry to a clinical trial, end of follow-up data, or the end of the study period (**31st December 2017**), whichever is earliest.

- Variables

Clinical and treatment characteristics:

- Demographic and clinical characteristics (medullary and extramedullary involvement, immunophenotype, cytogenetics, molecular biology) of patients at ALL diagnosis
- Clinical characteristics of patients prior to Blincyto initiation (prior treatment history (chemotherapy and hematopoietic stem cell transplantation (HSCT)) and response, minimal residual disease (MRD) results, mutation history)
- Clinical characteristics at Blincyto initiation (disease status, medullary and extramedullary involvement, immunophenotype, MRD results, cytogenetics, molecular biology, comorbidities)
- Concurrent ALL therapies during Blincyto treatment

Effectiveness:

- Complete remission (CR)/complete remission with partial recovery of peripheral blood counts (CRh*)/complete remission with incomplete recovery of peripheral blood counts (CRi)
- Relapse-free survival (RFS)
- MRD response
- Event free survival (EFS), disease free survival (DFS) and overall survival (OS)
- Receipt of allogeneic HSCT, incidence of acute and chronic Graft versus Host Disease (GvHD) ,graft failure rate
- 100-day mortality after allogeneic HSCT
- Subsequent immunotherapy or chemotherapy
- CD9 haematological relapse

Blincyto utilisation:

- Duration of treatment
- Number of cycles initiated
- Dosing schedule (starting dose and subsequent doses)
- Reasons for dose interruptions and reductions
- Administration of dexamethasone
- Reasons for discontinuation of Blincyto treatment
- Number of days of hospitalization (treatment related, other)
- Number of outpatient visits (treatment related, other)

Other covariates:

- HSCT conditioning regimen and donor type
- MRD level at HSCT
- Age at transplant

- Study Sample Size

The pool of eligible patients in the **five** countries is estimated to be approximately 400-500 B-precursor ALL patients. However, the actual number of patients that will be

included in the study will depend on the results of site feasibility, willingness of sites to participate in the study and availability of the medical records. It is not relevant to evaluate the precision of estimates for the primary objective. The secondary objectives would describe effectiveness, utilisation and safety endpoints in clinically relevant subgroups. For binary categorical outcomes, across a range (10-50%) of assumed proportions the width of the 95% confidence interval (CI) ranged between 18.6% and 31.0% for the smallest estimated subgroup sample size of 10 and a range of 3.1% to 5.2% for the largest estimated subgroup sample size of 350.

- Data Analysis

All analyses will be descriptive. Continuous variables will be summarised by mean, median, standard deviation, lower and upper quartiles, and minimum and maximum values. Categorical variables will be summarised by number and percentage of patients in each category. For categorical outcomes, 95% confidence intervals (CIs) will also be presented where appropriate. For time-to-event endpoints, Kaplan-Meier (KM) curves and KM proportions at select time points, the number of subjects with events and the number of subjects censored will be used to summarise the data. Analyses will be presented by the identified clinically relevant subgroups, country and year of Blincyto initation where groups are not less than 10 patients.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	**06 November 2017**	**See Summary of Changes**		
Superceding Amendment 1	**20 November 2017**	**See Summary of Changes**		

6. Milestones

Milestone	Planned date
Start of data collection*	**Q1 2018**
End of data collection*	**Q3** 2018
Final report of study results	Q2 2019

* These timelines are subject to receiving timely approvals from national competent authorities and ethics committees, which may vary by country.