18 December 2024
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Blincyto (Blinatumomab)
Treatment of acute lymphoblastic leukaemia
EU/3/09/650

Sponsor: Amgen Europe B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Blinatumomab
Other name(s)	--
International Non-Proprietary Name	Blinatumomab
Tradename	Blincyto
Orphan condition	Treatment of acute lymphoblastic leukaemia
Sponsor's details:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda Noord-Brabant Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Micromet AG
COMP opinion	2 June 2009
EC decision	24 July 2009
EC registration number	EU/3/09/650
Post-designation procedural history	
Sponsor's name change	From Micromet AG to Micromet GmbH – EC letter of 21/01/2012
Sponsor's name change	From Micromet GmbH to Amgen Research (Munich) GmbH – EC letter 19/06/2012
Transfer of sponsorship	From Amgen Research (Munich) GmbH to Amgen Europe BV – EC letter 13/02/2014
COMP opinion on review of orphan designation at the time of marketing authorisation	8 October 2015
COMP opinion on review of orphan designation at the time of type II variation (II/0011)	6 December 2018
COMP opinion on review of orphan designation at the time of type II variation (II/0030)	3 December 2020
Type II variation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Paolo Gasparini
Applicant	Amgen Europe B.V.
Application submission	13 February 2024
Procedure start	2 March 2024
Procedure number	EMA/H/C/003731/II/0056
Invented name	Blincyto

Proposed therapeutic indication	Extension of indication to include treatment as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL. Further information on Blincyto can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/blincyto
CHMP opinion	12 December 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Karri Penttila
Sponsor's report submission	27 March 2024
COMP discussion	3-5 December 2024
COMP opinion (adoption via written procedure)	18 December 2024

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2009 was based on the following grounds:

- for the purpose of orphan designation, the COMP considered that the indication should be broadened to "treatment of acute lymphoblastic leukaemia";
- of acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to be affecting approximately 1 in 10,000 persons in the Community, at the time the application was made;
- the condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy;
- although satisfactory methods of treatment of the condition have been authorised in the Community, sufficient justification has been provided that blinatumomab may be of significant benefit to those affected by the condition;

The COMP recommends the designation of this medicinal product, containing blinatumomab, as an orphan medicinal product for the orphan indication: treatment of acute lymphoblastic leukaemia.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2015 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;

- the prevalence of acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Blincyto may be of potential significant benefit to those affected by the orphan condition has been justified with clinical data showing the effectiveness in patients who are negative for the Philadephia gene and for whom there is no effective treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Blincyto, blinatumomab, EU/3/09/650 for treatment of acute lymphoblastic leukaemia is not removed from the Community Register of Orphan Medicinal Products.

2.3. Review of orphan medicinal product designation at the time of type II variation (II/0011)

The COMP opinion on the initial review of the orphan medicinal product designation in 2018 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.
- the prevalence of acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 1.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Blincyto is of significant benefit as it improves progression free survival and overall survival in patients with minimal residual disease in acute lymphoblastic leukaemia for which currently there is no authorised treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Blincyto, blinatumomab, EU/3/09/650 for acute lymphoblastic leukaemia is not removed from the Community Register of Orphan Medicinal Products.

2.4. Review of orphan medicinal product designation at the time of type II variation (II/0030)

The COMP opinion on the initial review of the orphan medicinal product designation in 2020 was based on the following grounds:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Blincyto may be of potential significant benefit in the treatment of patients who are double relapsed and refractory and for whom there are no further treatment options still holds.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Blincyto, blinatumomab, for treatment of acute lymphoblastic leukaemia (EU/3/09/650) is not removed from the Community Register of Orphan Medicinal Products.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Acute Lymphoblastic Leukaemia (ALL) continues to be described in the most recent WHO Classification and is represented by dedicated ICD code. ALL represents a biologically and clinically heterogeneous group of B/T-precursor-stage lymphoid cell malignancies arising from genetic insults that block lymphoid differentiation and drive aberrant cell proliferation and survival. In children, ALL is the commonest malignancy accounting for approximately 25 % of childhood cancer and it has 5-year event-free survival rates ranging between 76 % and 86 % in patients receiving protocol-based therapy. In adults, ALL is less common and generally carries a worse prognosis with a long-term survival probability less than 35–40 % (Curr Hematol Malig Rep (2012) 7:133–143). The condition continues to be designated by the COMP as a distinct medical entity.

The approved therapeutic indication(s) falls within the scope of the designated orphan condition "Treatment of acute lymphoblastic leukaemia":

- BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged ***1 month*** or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation.
- BLINCYTO is indicated as monotherapy for the treatment of paediatric patients aged ***1 month*** or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy (see section 4.2).
- ***BLINCYTO is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor ALL.***

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

ALL is a heterogeneous disease with outcomes dependent on patient age, mutational status and co morbid conditions.

Regardless of prognostic factors, the likelihood of initial remission is ≥ 95% in children and 70 to 90% in adults. About 75% of children and 30 to 40% of adults have continuous disease-free survival for 5 years and appear cured. Patients with ALL, refractory to induction or re-induction chemotherapy, have poor prognosis if they do not undergo HSCT. With induction therapy, some patients achieve complete remission but the majority of patients relapse. The long-term event-free survival of adult patients is only 30-35%.

Number of people affected or at risk

The sponsor has provided estimate of the prevalence based on the following databases were reviewed for information on cancer prevalence.

Acute Lymphoblastic Leukaemia (ALL):

- GLOBOCAN 2020
- NORDCAN 2019, 2020
- GLOBAL BURDEN OF DISEASE STUDY 2019
- NATIONAL CANCER REGISTRY OF IRELAND 2018, 2020
- DARWIN EU 2020
- SEER 2020
- PubMed (literature)
- EMBASE (literature)
- Google Scholar (literature)

In global and multi-national collaborative registry studies, all types of leukaemia are frequently analysed as a single entity, with no distinction made between acute and chronic leukaemia, or lymphoid or myeloid lineage subtypes, due to concerns about consistency of coding and classification across countries. Overall, ALL represents approximately 12-15% of all leukaemias (Redaelli 2005; Dong et al, 2020) and comprises about 25-33% of all childhood cancers and 80% of childhood leukaemias (Miranda-Filho et al, 2018), and approximately 5-10% of leukaemias in adults in Europe (Miranda-Filho et al, 2018). The current burden of ALL varies greatly across different countries and territories. In 2019, the age-standardized incidence rate was 6.27 per 100,000 in Western Europe. The incidence of ALL is strongly related to age with a bi-modal distribution resulting in a peak in risk in children less than 5 years of age and then a second peak occurring in the elderly (Du et al., 2022; Yi et al., 2020). The incidence of ALL in Europe for 2019 in the under 5 years of age group was 4.38 per 100,000 and then 6.81 per 100,000 in the greater than 70-year age group (IHME, 2020). There is also a gender preference in the incidence of ALL. It was reported the ratio of male to female incidence was about 1.54:1 (Yi et al., 2020).

According to the Global Burden of Disease data for 2019, the ALL prevalence for Europe ranged from 1.55 per 10,000 in eastern Europe to 5.42 per 10,000 in Western Europe with an overall prevalence for Europe as 3.46 per 10,000 (IHME, 2020).

In a study of Italian population-based cancer registries which represented 41% of the Italian population, data was extracted for multiple cancer types including precursor cell ALL, which resulted in 8,121 prevalent cases of ALL as of January 1, 2018 (Toffolutti et al., 2023). Using the UN population estimate (United Nations, 2022) of 59,877,426 to calculate the prevalence rate, the prevalence as of 2018 for Italy was 1.36 per 10,000.

The National Cancer Registry of Ireland (NCRI) reports 2-year, 5-year and 10-year ALL prevalence rates for 2018 as 0.20, 0.50 and 0.95 per 10,000 respectively (NCRI, 2023). For the year 2020, 2-year, 5-year and 10-year prevalence rates were 0.16, 0.45 and 0.86 per 10,000. Although prevalence rates for 2020 are more recent, the 2018 rates are included here to give context to the 2020 rates due to concerns of underreporting of cancer diagnoses during the COVID-19 pandemic for the years 2019 and 2020.

The NORDCAN data reports the complete prevalence of ALL in 2020 for the Nordic countries as 3.16 per 10,000 for males and 2.61 per 10,000 for females with an overall prevalence of 2.89 per 10,000 (NORDCAN Cancer Fact Sheet, 2022). The sponsor has also proposed a second estimate based on the subpopulation of B-ALL they are targeting in their indication and reviewed reports published by DARWIN. The COMP noted these estimates but focussed on the registry sources.

The COMP considered the review of the challenges associated with the estimation of prevalence of ALL as comprehensive. In view of the uncertainties of the validity of member-state specific estimates for the EU+EAA, the COMP accepted a prevalence estimate for ALL of approximately 2 in 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor has provided a table with products which are authorised for treatment of B-ALL in Europe.

Table 1. Authorised Targeted Treatments for B-ALL (excluding treatments specifically indicated for Philadelphia chromosome positive B-ALL)

Product **Treatment Schema**
Adults **Inotuzumab ozogamicin (Besponsa SmPC, 2022)** Adults with relapsed or refractory CD22-positive B cell precursor ALL. Adult patients with Philadelphia chromosome positive relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 TKI Monotherapy **Brexucabtagene autoleucel (Tecartus SmPC, 2023)** Adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL Monotherapy
Children and young adults **Clofarabine** (Evoltra SmPC, 2023) Paediatric patients with ALL who have relapsed or are refractory after receiving at least 2 prior regimens and where there is no other treatment option anticipated to result in a durable response. Monotherapy **Tisagenlecleucel** (Kymriah SmPC, 2023) Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second or later relapse. Monotherapy

Table 2. The following products targeted specific subgroups (either molecular or age-groups): Kymriah, Evoltra, Tecartus, Besponsa) are not be considered satisfactory methods as they are not indicated for the entirety of the target population of Blincyto.

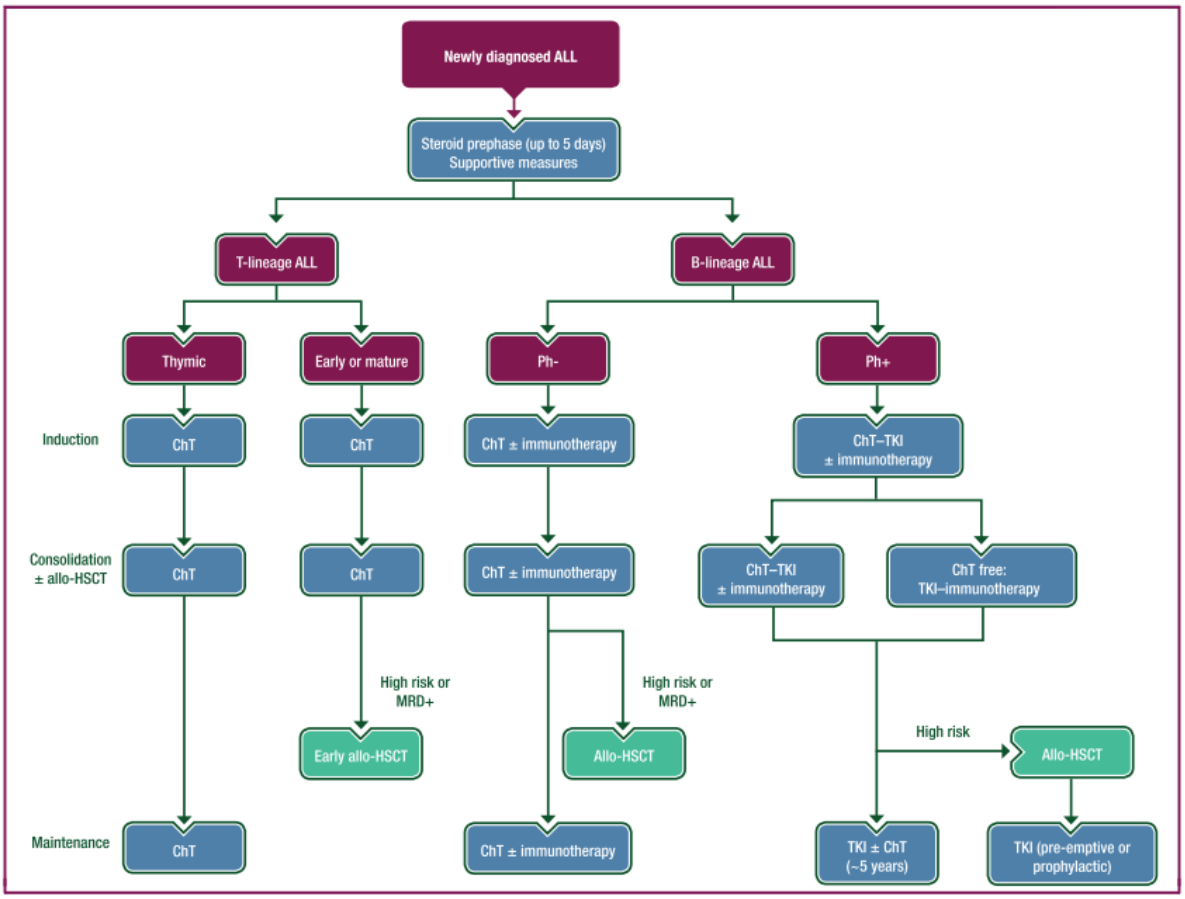
Active Substance (Product)	**Authorisation**	**Indication**
Asparaginase (Generic product)	National authorisations	Indicated as a component of an anti-neoplastic combination therapy of ALL in children and adult
Blinatumomab (BLINCYTO)	Centralized (EU/1/15/1047)	As monotherapy for the treatment of adults with CD19 positive relapsed or refractory B precursor ALL. Patients with Ph+ B-precursor ALL should have failed treatment with at least 2 TKIs and have no alternative treatment options. As monotherapy for the treatment of adults with Ph- CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%. As monotherapy for the treatment of paediatric patients aged 1 year or older with Ph- CD19 positive B precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic haematopoietic stem cell transplantation. As monotherapy for the treatment of paediatric patients aged 1 year or older with high-risk first relapsed Ph- CD19 positive B-precursor ALL as part of the consolidation therapy.
Brexucabtagene autoleucel (Tecartus)	Centralized (EU/1/20/1492)	Treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL
Clofarabine (Evoltra*)	Centralized (EU/1/06/334)*	ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.
Crisantaspase (L-asparaginase from Erwinia chrysanthemi) (Erwinase*)	MRP*	Used in combination with other chemotherapeutic agents, for the treatment of patients, mainly children, with acute lymphoblastic leukaemia who have developed hypersensitivity (clinical allergy or silent inactivation) to native or pegylated asparaginase derived from E. coli.
Cylcophosphamide (generic products)	Various national and MR authorisations	Cyclophosphamide may be used alone or in combination with other chemotherapeutic agents, depending on the indication. Cyclophosphamide is indicated in the treatment of ALL.
Cytarabine (generic products)	Various national and MR authorisations	Alone or in combination for induction of remission in acute myeloid leukaemia in adults and for other acute leukaemias of adults and children.

Active Substance (Product)	Authorisation	Indication
Dasatinib (Sprycel*)	Centralized (EU/1/06/363)*	Treatment of adult patients with Ph+ ALL with resistance or intolerance to prior therapy. Treatment of paediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy.
Daunorubicin hydrochloride (generic products)	Various national and MR authorisations	As an antimitotic and cytotoxic for the induction of remissions in ALL. As part of combination regimen, is indicated for the treatment of ALL in children
Dexamethasone phosphate (generic products)	Various national and MR authorisations	In combination with other medicines, treatment of ALL
Doxorubicin hydrochloride (generic products)	Various national and MR authorisations	Indicated in the following neoplastic conditions: ALL
Idarubicin hydrochloride (generic products)	Various national and MR authorisations	Treatment of relapsed ALL as second line treatment in adults and children.
Imatinib mesilate (Glivec*)	Centralized (EU/1/01/198)*	Treatment of - adult and paediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy. - adult patients with relapsed or refractory Ph+ ALL as monotherapy.
Inotuzumab ozogamicin (Besponsa)	Centralized (EU/1/17/1200)	As monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor ALL. Adult patients with Ph+ relapsed or refractory B cell precursor ALL should have failed treatment with at least 1 TKI.
Mercaptopurine (generic authorisations)	Various national and MR authorisations	Treatment of acute leukaemia in adults, adolescents and children
Mercaptopurine (oral suspension) (Xaluprine)	Centralized (EU/1/11/727)	Treatment of ALL in adults, adolescents and children
Methotrexate (generic products)	Various national and MR authorisations	Maintenance therapy in ALL in adults, adolescents and children aged 3 years and over.

Active Substance (Product)	Authorisation	Indication
Nelarabine (Atriance)	Centralized (EU/1/07/403)	Treatment of patients with T-cell ALL whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.
Pegaspargase (Oncaspar)	Centralized (EU/1/15/1070)	Indicated as a component of antineoplastic combination therapy in ALL in paediatric patients from birth to 18 years, and adult patients.
Ponatinib (Iclusig)	Centralized (EU/1/13/839)	Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
Prednisolone (generic products)	National and MR authorisations	Prednisolone is an established component of chemotherapeutic regimes used in the treatment of the following neoplasms: ALL (including the acute blastic phase of myeloid leukaemia resembling acute lymphoblastic leukaemia)
Tioguanide (e.g. Lanvis)	National and MR authorisations	Treatment of leukaemias, particularly acute myeloblastic leukaemia and acute lymphoblastic leukaemia
Tisagenlecleucel (Kymriah)	Centralized (EU/1/18/1297)	Treatment of paediatric and young adult patients up to and including 25 years of age with B cell ALL that is refractory, in relapse post-transplant or in second or later relapse.
Vincristine sulfate (generic products)	National authorisations	Treatment of acute leukaemias
Vindesine sulfate (generic products)	National authorisations	In combination with other oncolytic drugs for remission or consolidation therapy in ALL

Recently a revised European guidance has been published regarding ALL: ESMO Clinical Practice Guideline interim update on the use of targeted therapy in acute lymphoblastic leukaemia Ann Oncol. 2024;35(1):15-28. A treatment algorithm is proposed which could be applicable to this case.

Figure 1. Treatment algorithm for newly diagnosed ALL.



Purple: general categories or stratification; blue: systemic anticancer therapy; turquoise: combination of treatments or other systemic treatments; white: other aspects of management. Systemic ChT should be accompanied by intrathecal ChT for prevention of CNS relapse in all patient categories. ALL, acute lymphoblastic leukaemia; allo-HSCT, allogeneic haematopoietic stem cell transplantation; ChT, chemotherapy; CNS, central nervous system; MRDþ, minimal residual disease positive; Ph+, Philadelphia chromosome positive; Ph-, Philadelphia chromosome negative; TKI, tyrosine kinase inhibitor.

Significant benefit

The sponsor is proposing that their product can offer a significant benefit in newly diagnosed B-cell precursor ALL patients who are in the consolidation phase of treatment and whose disease is Philadelphia chromosome negative CD19 positive. According to current recommendations these patients can be treated with a broad group of chemotherapeutic medicines and immunotherapy (please see Existing Methods, Figure 1)

The COMP noted that two studies submitted provided data to assess the claim of a clinically relevant advantage.

- The first study, **Study E1910 (also known as Study 20129152)** is an ongoing phase 3, randomized, controlled study investigating the efficacy and safety of blinatumomab in combination with consolidation chemotherapy compared with consolidation chemotherapy alone in adult

subjects (>30 through >70 years of age) with newly diagnosed Philadelphia chromosome-negative B-cell precursor ALL.

- The second study, **Study 20120215** was a phase 3, open label, randomised, controlled, multicentre study investigating the efficacy and safety of blinatumomab as consolidation therapy versus intensive standard of care late consolidation chemotherapy in paediatric subjects (> 28 days and < 18 years of age) with high-risk first relapsed B-cell precursor ALL (as defined by the I-BFM Study Group and IntReALL Consortium Risk Classification).

Study E1910 (also known as Study 20129152)

In study E1910 eligible subjects initially received 2.5 months of combination induction chemotherapy with extended remission induction, addition of pegaspargase for subjects < 55 years of age, and the addition of rituximab for CD20-positive subjects. Subjects in each arm received the same number of cycles and doses of chemotherapy. Following the US Food and Drug Administration (FDA) accelerated approval of blinatumomab for MRD-positive ALL in March 2018, subjects who were MRD-positive after intensification therapy were assigned to the blinatumomab arm (Arm C) of the study and were no longer randomized.

Following completion of consolidation chemotherapy with or without blinatumomab, subjects were given 2.5 years of POMP maintenance therapy (6-mercaptopurine, vincristine, methotrexate, and prednisone) timed from the start of the intensification cycle (step 4, Arm E). In lieu of consolidation and maintenance chemotherapy, subjects could proceed to allogeneic HSCT at the discretion of the treating physician, which was suggested to be done after the first 2 cycles of blinatumomab in the blinatumomab arm or at any time following intensification chemotherapy in the control chemotherapy arm. One hundred and fifty patients were included in the maintenance part of the trial.

The multi-agent chemotherapy regimens used for induction, intensification, consolidation, and maintenance therapy in Study E1910 were based on the UKALL12/ECOG2993 protocol, which is recognized as standard of care (SOC) for these patients (NCCN, 2023; Goldstone et al, 2008).

Primary endpoints for this study are summarized in Table 3.

Table 3 Primary endpoints for Study E1910

Primary	
• To compare overall survival (OS) of subjects with BCR-ABL-negative B cell precursor ALL who are MRD negative (based on multiparameter flow cytometric [MFC] assessment of residual blasts) treated with blinatumomab and chemotherapy to those subjects treated with chemotherapy alone following induction and intensification chemotherapy.	• OS measured as time from randomization until death due to any cause. Subjects alive will be censored at the date last known to be alive.

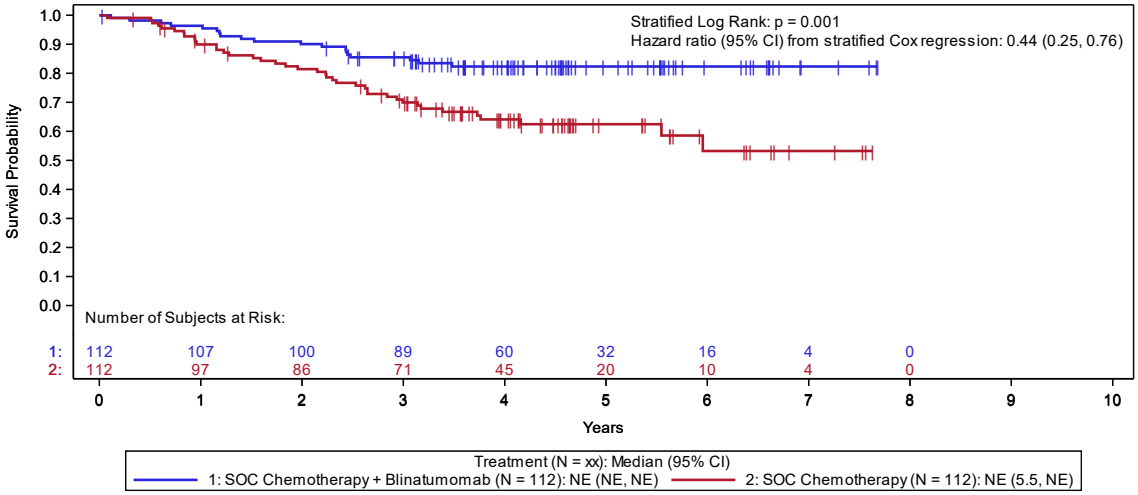
Overall Survival

MRD-negative Subjects – Primary Endpoint

The median follow-up time for OS was 4.5 years in both the SOC chemotherapy alternating with blinatumomab arm and the SOC chemotherapy arm. The study achieved its **primary endpoint**, with OS being statistically significantly improved in the SOC chemotherapy alternating with blinatumomab arm compared with the SOC chemotherapy arm (p = 0.001 by the 1-sided stratified log-rank test). The OS stratified hazard ratio from a Cox regression model was 0.44 (95% CI: 0.25, 0.76), indicating

a 56% reduction in the hazard rate for OS in the SOC chemotherapy alternating with blinatumomab arm (Figure 2). The median OS was not reached in either treatment arm. The KM estimate of OS at 5 years was 82.4% (95% CI: 73.7, 88.4) in the SOC chemotherapy alternating with blinatumomab arm and 62.5% (95% CI: 52.0, 71.3) in the SOC chemotherapy arm.

Figure 2. Kaplan-Meier for Overall Survival for MRD-negative at Randomization (Step 3) – Study E1910 Primary Analysis (Full Analysis Set)



MRD = minimal residual disease
Censor indicated by vertical bar.
Step 3 randomization date is the reference date for analysis of the primary OS endpoint (protocol objective 2.1.1).

Study 20120215

This was a phase 3, open label, randomised, controlled, multicentre study investigating the efficacy and safety of blinatumomab as consolidation therapy versus intensive standard of care late consolidation chemotherapy in paediatric subjects (> 28 days and < 18 years of age) with high-risk first relapsed B-cell precursor ALL (as defined by the I-BFM Study Group and IntReALL Consortium Risk Classification). Subjects were risk stratified by the following stratification factors at randomisation:

- age: 1 to 9 years; other (<1 year and > 9 years)
- bone marrow/MRD: M1 with MRD level < 10-3; ≥ M1 with MRD level 10-3; and M2

Following induction and 2 blocks of high-risk consolidation therapy, eligible high-risk subjects could enter Study 20120215 as a third consolidation therapy. After a screening period of up to 3 weeks, eligible subjects were enrolled and randomized into 1 of the following 2 treatment groups:

- Blinatumomab arm: 1 consolidation cycle of blinatumomab (15 µg/m2/day [maximum daily dose was not to exceed 28 µg/day]), defined as a 4-week cIV infusion of blinatumomab
- HC3 arm: 1 consolidation cycle of HC3, defined as 1 week of treatment with HC3 and 3 weeks of no treatment. High-risk consolidation 3 chemotherapy was administered per the IntReALL protocol.

The study consisted of a 3-week screening period, a 4-week treatment period followed by a 1-week safety follow-up period, a 12-month short-term efficacy follow-up, and a long-term follow-up that continued until the last subject on study was either followed for 36 months after receiving allogeneic HSCT or until death, whichever occurred first. After reaching the primary endpoint, subjects were followed in the long-term follow-up period.

The study was conducted in Australia, Belgium, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Portugal, Spain and United Kingdom.

Efficacy Analysis

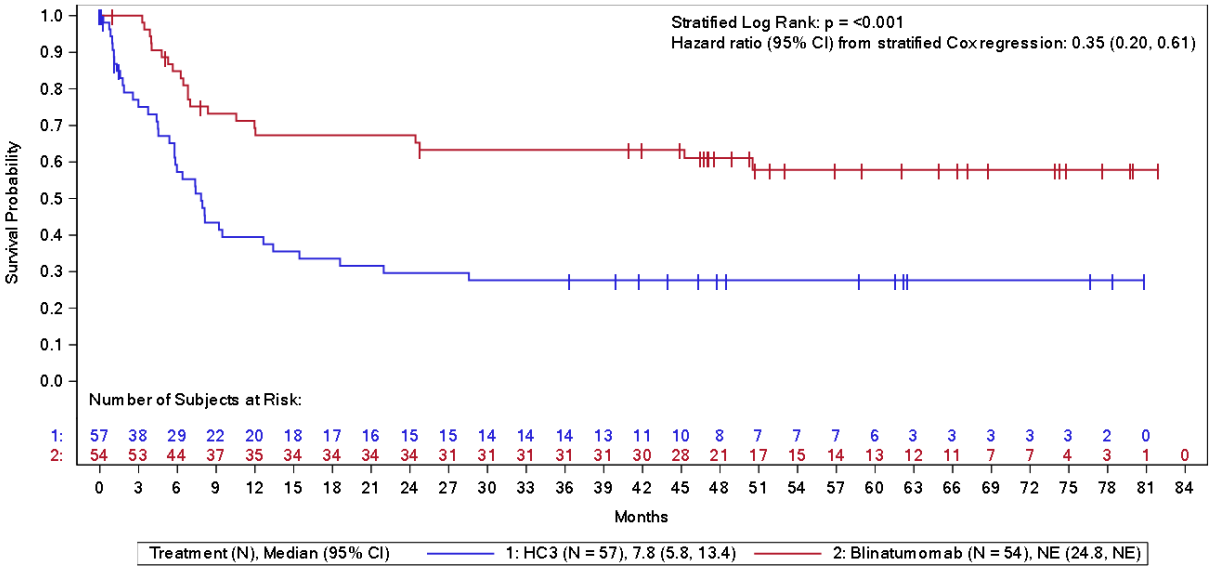
The primary objective was event free survival (EFS) after blinatumomab when compared to SOC. Overall Survival (OS) was a key secondary objective. Final analysis results with a data cut-off date of 21 November 2022 are summarized below. The following sections provide a summary of the primary and secondary efficacy endpoints of this study.

Event-free Survival

The median follow-up time for EFS was 51.9 months (95% CI: 47.2, 62.1). Event free survival was statistically significantly improved in the blinatumomab arm compared with the HC3 arm ($p < 0.001$ by the 2 sided, stratified log-rank test). The EFS hazard ratio from a stratified Cox proportional hazard model was 0.35 (95% CI: 0.20, 0.61), indicating a 65% risk reduction in the blinatumomab arm (Figure 3). The Kaplan-Meier median time to event was 7.8 months (95% CI: 5.8, 13.4) in the HC3 arm and was not reached in the blinatumomab arm. The 5-year Kaplan-Meier estimate for EFS was 27.6% (95% CI: 16.2, 40.3) in the HC3 arm and 57.8% (95% CI: 42.5, 70.4) in the blinatumomab arm.

Figure 3. Kaplan-Meier for Event-free Survival (Full Analysis Set) –

Study 20120215 Final Analysis



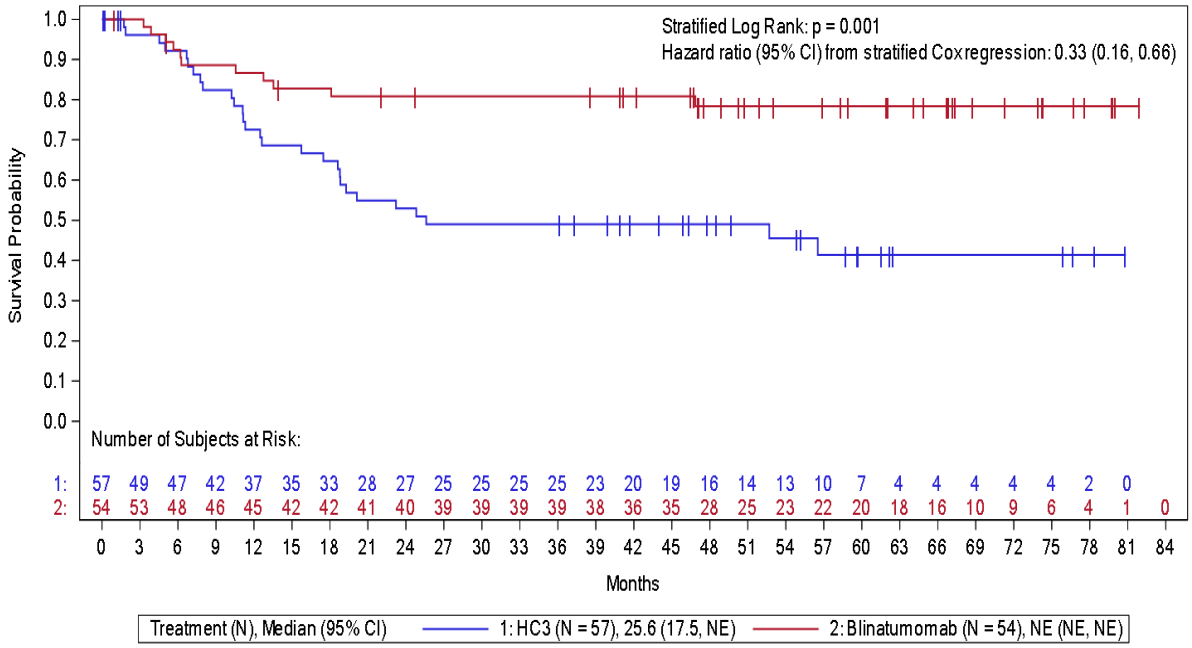
N = Number of subjects in the analysis set. CI = Confidence Interval. NE = Not estimable. Censor indicated by vertical bar |.

HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable. Censor indicated by vertical bar.

Overall Survival

The median follow-up time for OS was 55.2 months (95% CI: 48.5, 62.0). The OS hazard ratio from a stratified Cox proportional hazard model was 0.33 (95% CI: 0.16 to 0.66), indicating 67% risk reduction in the blinatumomab arm (Figure 5). The median OS (95% CI) was 25.6 months (95% CI: 17.5, not estimable [NE]) in the HC3 arm and not reached in the blinatumomab arm. The 5-year Kaplan-Meier estimate was 41.4% (95% CI: 26.3, 55.9) in the HC3 arm and 78.4% (95% CI: 64.2, 87.4) in the blinatumomab arm.

Figure 4. Kaplan-Meier for Overall Survival (Full Analysis Set) – Study 20120215 Final Analysis



HC3 = high-risk consolidation 3 chemotherapy; NE = not estimable. Death events which occurred after the end of study are also included as the overall survival event. Censor indicated by vertical bar.

A sensitivity analysis was performed to estimate latent treatment effect adjusted for subjects in the HC3 arm who were dropped in the blinatumomab arm (Branson and Whitehead, 2002). This analysis produced a hazard ratio of 0.24 (95% CI: 0.11, 0.55), which was numerically lower than that reported for the overall population (0.33; 95% CI: 0.16, 0.66).

Overview of findings

Improved Overall Survival

In Study E1910, OS was statistically significantly improved in the blinatumomab alternating with chemotherapy arm compared with the chemotherapy arm for subjects with MRD-negative B cell precursor ALL (the primary endpoint). Consolidation therapy with blinatumomab alternating with chemotherapy was also associated with improved OS compared with chemotherapy alone for subjects with MRD-positive B cell precursor ALL.

In Study 20120215, OS was improved in the blinatumomab arm compared with the HC3 arm for paediatric subjects with high-risk first relapsed ALL.

In conclusion, the sponsor has provided clinical data showing an improvement in event free events and overall survival when blinatumomab is added on to the recommended standard of care in both adult and paediatric populations. This add on improvement in survival endpoints across several studies, which form the basis for the new therapeutic indication for both paediatric and adult patients, with relevant additional characteristics (with or without residual disease and across several disease states (newly diagnosed or 1st relapse) is accepted as a clinically relevant advantage.

4. COMP position adopted on date

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acute lymphoblastic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening depending on the response to treatment, being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent anaemia, bleeding, infections and fatigue are linked to the underlying bone marrow failure.
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the claim that Blincyto is of significant benefit to those affected by the orphan condition is established based on improved survival outcomes achieved in newly diagnosed adult and in younger paediatric patients with relapsed disease when Blincyto is added to standard consolidation treatment.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Blincyto, blinatumomab for Treatment of acute lymphoblastic leukaemia (EU/3/09/650) is not removed from the Community Register of Orphan Medicinal Products.