Sponsor: Sanofi **Drug substance(s):** clofarabine	**Study code:** CLOFAL06952 (OBS15637)
Title of the study: Drug Use Investigation of Evoltra® for Acute Lymphoblastic Leukemia (ALL) patients.	
Study period: Registry initiation date [first patient in (FPI)]: 18th September 2013 Registry completion date [last patient out (LPO)]: 19th September 2018 Study Status: Completed	
Phase of development: NA	
Objectives: To collect information on the safety and effectiveness of Evoltra® in the actual clinical setting in patients with acute lymphoblastic leukemia (ALL), and identify the following: [1] Unexpected adverse drug reactions [2] Occurrence of the adverse drug reactions in real clinical practice. [3] Factors that could affect the safety of the drug [4] Occurrence of the intensive survey items (hematotoxicity, infection, renal disorders, hepatobiliary disorders, capillary leak syndrome (CLS) and systemic inflammatory response syndrome (SIRS), tumour lysis syndrome, and cardiovascular events) [5] Factors that could affect the effectiveness of the drug	
Methodology: All patients treated with Evoltra were registered for this post-marketing surveillance (multicenter, noncontrolled, non-comparative, observational study) started in June 2013. Data collection was conducted using the paper CRF. **No. of patients:** 120 patients (21 years old and younger) with relapsed/refractory ALL were planned to be registered (100 patients as the safety analysis population). **Rationale for no. of patients:** Based on the assumption of detecting 3% cases of SIRS and CLS with a confidence level of 95%, 100 patients are calculated. Then, considering 15% of dropout rate in safety analysis set, at least 120 ALL patients are necessary. **Inclusion Criteria:** All patients treated with Evoltra **Exclusion Criteria:** NA **No. of Centers:** All Evoltra administered centers where will be contracted. **Observation period:** "Evoltra is administered daily for 5 consecutive days, then discontinued at least for 9 days" is defined as a cycle. Observation period is from initial administration of the drug to the end of final cycle, until 6 cycles as maximum. **Safety:** The information on the adverse events (AEs), the serious AE (SAEs), relationship to Evoltra, grade of toxicity, outcomes and abnormal changes in clinical laboratory parameters (hematology and clinical chemistry) were collected.	

Effectiveness: To evaluate the effectiveness, a modified version of the COG (Children's Oncology Group) standard was used, and the investigator judged it according to the following standard at the end of the final cycle. The effectiveness was evaluated by the best over-all response (CR, CRp or PR), and the effectiveness rate was evaluated by CR+CRp+PR.

Complete remission (CR): Meet all of the following conditions:

- No leukemic cells are found in the peripheral blood, and no extramedullary infiltration
- Less than 5% of leukemia cells in bone marrow
- Platelet count and neutrophil count in peripheral blood have recovered to ≧100,000/mm^3 and ≧1,000/mm3, respectively

Complete remission without recovery of platelet count (CRp):

- Meet all CR criteria except platelet count recovery (≧100,000/mm3)

Partial remission (PR):

- No leukemic cells are found in peripheral blood
- Leukemic cells in bone marrow are 5% or more and 25% or less, and normal blood cell precursors are observed. Or if less than 5% of leukemic cells in bone marrow, but do not meet the criteria for CR and CRp

Ineffective: do not meet the criteria for CR, CRp and PR

Statistical analysis: The following items were aggregated or analyzed.

1. Patient disposition
1) No. of cases enrolled and CRF collected
2) No. of cases for safety and effectiveness analysis
3) No. of cases excluded from analysis, and reasons
2. Safety
1) Incidence of ADRs
2) Incidence of intensive survey items
3) Factors that may affect safety (incidence of ADRs by patient background)
3. Effectiveness
1) The best over-all response (CR, CRp or PR), and rate of CR+CRp+PR
2) Factors that may affect effectiveness
4. Patients with specific backgrounds
1) Safety and effectiveness in pediatrics, elderly, pregnant woman, patients with hepatic disorders, and patients with renal disorders

Treatment:

Marketed Evoltra was used as treatment product.

Follow the “Dosage and administration” of package insert in Japan:

Usually the dose of 52 mg/m^2 (body surface area) of clofarabine is administered as an intravenous infusion over 2 hours daily for 5 consecutive days, then discontinued at least for 9 days as a cycle.

And repeat cycles. The dose of clofarabine can be decreased according to the patient condition.

Summary Results:

Participants (actual):

In total, 264 patients from 115 sites were registered, and 262 CRFs were collected. The safety analysis population was comprised of 260 patients, 2 patients (2: CRFs were filled out by nonregistered doctors) were excluded from the safety analysis. The effectiveness population was consisted of 225 patients, 35 patients* (34: off-label use, 2: recorded as “unknown” in the effectiveness assessment) were excluded from the effectiveness analysis. (Fig. 1)

*: Multiple reasons could be attributed to each of the patients excluded from effectiveness analysis

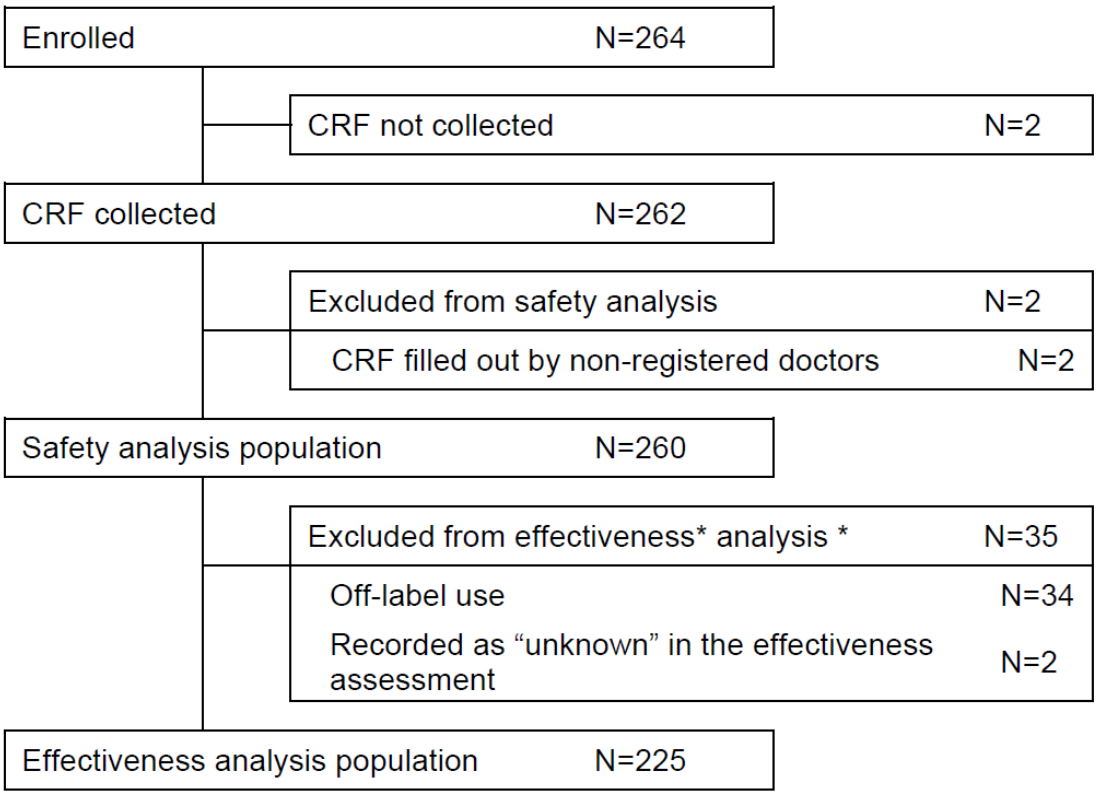

Fig. 1 Patient disposition

*: Multiple reasons could be attributed to each of the patients excluded from effectiveness analysis

Participant characteristics and primary analyses:

Baseline characteristics

The baseline characteristics were as follows;

The numbers of male and female patients were 157 (60.38%) and 103 (39.62%), respectively. Age (mean±S.D.) was 22.5±19.0 years old (median: 16.0 years old, min. – max.: 0 – 73 years old). The number of patients diagnosed with relapsed/refractory acute lymphoblastic leukemia (ALL) was 226 (86.92%). Body surface area (mean±S.D.) was 1.27±0.43 m2 (median: 1.35 m2, min. – max.: 0.3 – 2.0 m^2). 116 patients (44.62%) had any complications. The numbers of patients with complications of liver dysfunction and renal dysfunction were 33 (12.69%) and 10 (3.85%), respectively. Most patients were treated with Evoltra for one cycle [162 patients (62.31%) for 1 cycle, 65 patients (25.00%) for 2 cycles, 20 patients (7.69%) for 3 cycles, 7 patients (2.69%) for 4 cycles, 2 patients (0.77%) for 5 cycles, 4 patients (1.54%) for 6 cycles].

Safety

In the safety analysis set, ADRs were observed in 217 of the 260 patients (83.46%) shown in Table 1. The most common ADRs observed were platelet count decreased 42.69% (n=111), anaemia 33.85% (n=88), white blood cell count decreased 33.08% (n=86), neutrophil count decreased 26.54% (n=69) and febrile neutropenia 25.38% (n=66). Serious ADRs were observed in 170 of the 260 patients (65.38%). The most common serious ADRs observed were platelet count decreased 26.92% (n=70), white blood cell count decreased 22.69% (n=59), febrile neutropenia 19.62% (n=51), neutrophil count decreased 18.08% (n=47) and anaemia 16.54% (n=43).

Table 1 Incidence of ADRs in patients of safety analysis population

Total patient number	260	
Number of patients with ADRs	217	
Incidence of ADRs (%)	83.46%	
ADRs (**SOC**/PT)	N	(%)
Infections and infestations	50	(19.23)
Bacteraemia	2	(0.77)
Bronchopulmonary aspergillosis	1	(0.38)
Cellulitis	2	(0.77)
Cytomegalovirus infection	1	(0.38)
Endotoxic shock	1	(0.38)
Escherichia sepsis	1	(0.38)
Fungal infection	1	(0.38)
Herpes zoster	6	(2.31)
Human herpesvirus 6 infection	1	(0.38)
Infection	6	(2.31)
Pneumonia	6	(2.31)
Pneumonia adenoviral	1	(0.38)
Pneumonia cytomegaloviral	1	(0.38)
Pulmonary mycosis	1	(0.38)
Sepsis	15	(5.77)
Septic shock	1	(0.38)
Upper respiratory tract infection	1	(0.38)

ADRs (**SOC**/PT)	N	(%)
Varicella	1	(0.38)
Streptococcal sepsis	2	(0.77)
Systemic mycosis	1	(0.38)
Klebsiella sepsis	1	(0.38)
Staphylococcal sepsis	1	(0.38)
Adenoviral haemorrhagic cystitis	1	(0.38)
Cytomegalovirus viraemia	1	(0.38)
Viral haemorrhagic cystitis	1	(0.38)
Bacterial infection	1	(0.38)
Lung infection	1	(0.38)
Pleural infection	1	(0.38)
Respiratory syncytial virus infection	1	(0.38)
Device related infection	3	(1.15)
Cystitis viral	2	(0.77)
Aspergillus infection	1	(0.38)
Varicella zoster pneumonia	1	(0.38)
Blood and lymphatic system disorders	142	(54.62)
Anaemia	88	(33.85)
Disseminated intravascular coagulation	2	(0.77)
Febrile neutropenia	66	(25.38)
Leukopenia	5	(1.92)
Neutropenia	13	(5.00)
Pancytopenia	6	(2.31)
Thrombocytopenia	6	(2.31)
Histiocytosis haematophagic	1	(0.38)
Haematotoxicity	5	(1.92)
Bone marrow failure	11	(4.23)
Cytopenia	3	(1.15)
Metabolism and nutrition disorders	18	(6.92)
Glucose tolerance impaired	1	(0.38)
Hypercalcaemia	1	(0.38)
Hyperglycaemia	1	(0.38)
Hypocalcaemia	1	(0.38)
Hypokalaemia	4	(1.54)
Hypomagnesaemia	1	(0.38)
Hyponatraemia	2	(0.77)
Tumour lysis syndrome	10	(3.85)
Decreased appetite	1	(0.38)

ADRs (**SOC**/PT)	N	(%)
Nervous system disorders	8	(3.08)
Altered state of consciousness	1	(0.38)
Epilepsy	1	(0.38)
Headache	5	(1.92)
Peripheral sensory neuropathy	1	(0.38)
Seizure	1	(0.38)
Cardiac disorders	3	(1.15)
Pericardial effusion	3	(1.15)
Vascular disorders	8	(3.08)
Capillary leak syndrome	6	(2.31)
Hypertension	2	(0.77)
Respiratory, thoracic and mediastinal disorders	7	(2.69)
Acute respiratory distress syndrome	1	(0.38)
Dyspnoea	1	(0.38)
Pleural effusion	2	(0.77)
Respiratory disorder	1	(0.38)
Respiratory failure	2	(0.77)
Tachypnoea	1	(0.38)
Gastrointestinal disorders	34	(13.08)
Abdominal pain	3	(1.15)
Diarrhoea	5	(1.92)
Lip swelling	1	(0.38)
Nausea	11	(4.23)
Pancreatitis	2	(0.77)
Pancreatitis acute	2	(0.77)
Proctalgia	1	(0.38)
Stomatitis	6	(2.31)
Vomiting	8	(3.08)
Oral disorder	1	(0.38)
Hepatobiliary disorders	38	(14.62)
Hepatic function abnormal	23	(8.85)
Hepatic pain	1	(0.38)
Hyperbilirubinaemia	1	(0.38)
Jaundice	1	(0.38)
Liver disorder	10	(3.85)
Venoocclusive liver disease	1	(0.38)
Hepatobiliary disease	1	(0.38)
Drug-induced liver injury	1	(0.38)

ADRs (**SOC**/PT)	N	(%)
Skin and subcutaneous tissue disorders	7	(2.69)
Erythema	1	(0.38)
Palmar erythema	1	(0.38)
Palmar-plantar erythrodysaesthesia syndrome	1	(0.38)
Rash	3	(1.15)
Urticaria	1	(0.38)
Musculoskeletal and connective tissue disorders	1	(0.38)
Pain in extremity	1	(0.38)
Renal and urinary disorders	9	(3.46)
Haematuria	1	(0.38)
Renal failure	1	(0.38)
Renal tubular disorder	1	(0.38)
Renal impairment	3	(1.15)
Acute kidney injury	5	(1.92)
Reproductive system and breast disorders	1	(0.38)
Genital ulceration	1	(0.38)
General disorders and administration site conditions	33	(12.69)
Chest pain	1	(0.38)
Chills	2	(0.77)
Death	1	(0.38)
Face oedema	1	(0.38)
Generalised oedema	1	(0.38)
Malaise	2	(0.77)
Mucous membrane disorder	4	(1.54)
Oedema	1	(0.38)
Oedema peripheral	2	(0.77)
Pain	2	(0.77)
Pyrexia	16	(6.15)
Localised oedema	1	(0.38)
Systemic inflammatory response syndrome	8	(3.08)
Multiple organ dysfunction syndrome	1	(0.38)
Investigations	153	(58.85)
Alanine aminotransferase increased	39	(15.00)
Aspartate aminotransferase increased	32	(12.31)
Blood bilirubin increased	7	(2.69)
Blood creatine phosphokinase increased	1	(0.38)
Blood creatinine increased	2	(0.77)
Blood potassium decreased	1	(0.38)
C-reactive protein increased	2	(0.77)

Electrocardiogram QT prolonged	1	(0.38)
Gamma-glutamyltransferase increased	4	(1.54)

ADRs (**SOC**/PT)	N	(%)
Haemoglobin decreased	8	(3.08)
Lymphocyte count decreased	7	(2.69)
Neutrophil count decreased	69	(26.54)
Platelet count decreased	111	(42.69)
White blood cell count decreased	86	(33.08)
Transaminases increased	3	(1.15)
Blood alkaline phosphatase increased	1	(0.38)
Hepatic enzyme increased	4	(1.54)
Liver function test increased	2	(0.77)

N: number of patients

ADRs were categorized by the ICH Medical Dictionary for Regulatory Activities (MedDRA) Ver. 22.1.

[Factors possibly influencing the safety]

The incidence of ADRs by factors possibly influencing the safety in all patients and in the patients with relapsed/refractory ALL were shown in Table 2 and Table 3, respectively.

Table 2 Incidence of ADRs by factors possibly influencing the safety in all patients (safety analysis population)

Factors		N	N with ADRs	(%)
Total		260	217	(83.46)
Age (pediatrics)	<15 years	124	104	(83.87)
	≧15 years	133	112	(84.21)
	Unknown	3	1	(33.33)
Age (elderly)	<65 years	245	205	(83.67)
	≧65 years	12	11	(91.67)
	Unknown	3	1	(33.33)
Diagnosis (Reason for use)	Relapsed/refractory ALL	226	187	(82.74)
	Others	34	30	(88.24)
Sex	Male	157	133	(84.71)
	Female	103	84	(81.55)
Previous medical history	Yes	94	81	(86.17)
	No	166	136	(81.93)
Complications	Yes	116	104	(89.66)
	No	144	113	(78.47)
Complication (Hepatic disorder)	Yes	33	31	(93.94)
	No	227	186	(81.94)
Complication (Renal disorder)	Yes	10	7	(70.00)
	No	250	210	(84.00)
No. of Evoltra treatment cycles	1 cycle	162	137	(84.57)
	2 cycles	65	56	(86.15)
	3 cycles	20	14	(70.00)
	4 cycles	7	5	(71.43)
	5 cycles	2	2	(100.00)
	6 cycles	4	3	(75.00)

Factors		N	N with ADRs	(%)
Total		260	217	(83.46)
Concomitant treatment for the target disease	Yes	180	156	(86.67)
	No	80	61	(76.25)
Hematopoietic stem cell transplantation	Yes	2	2	(100.00)
	No	258	215	(83.33)
Radiation therapy	Yes	2	2	(100.00)
	No	258	215	(83.33)
Concomitant medication for the target disease	Yes	179	155	(86.59)
	No	81	62	(76.54)

N: number of patients

Table 3 Incidence of ADRs by factors possibly influencing the safety in the patients with relapsed/refractory ALL (safety analysis population)

Factors		N	N with ADRs	(%)
Total		226	187	(82.74)
Age	<22 years	140	115	(82.14)
	≧22 years	84	72	(85.71)
	Unknown	2	0	(0.00)
Duration of the disease (year)	<1 year	76	63	(82.89)
	1≦ < 3 years	88	72	(81.82)
	3≦ < 5 years	34	29	(85.29)
	≧5 years	24	21	(87.50)
	Unknown	3	2	(66.67)
	NR	1	0	(0.00)
French-American-British (FAB) classification at the disease onset	L1	125	104	(83.20)
	L2	70	56	(80.00)
	L3	9	9	(100.00)
	Others	4	4	(100.00)
	Unknown	9	8	(88.89)
	NR	9	6	(66.67)
Type of leukemia cells at the disease onset	B cell	184	152	(82.61)
	T cell	34	30	(88.24)
	Others	8	5	(62.50)
Philadelphia chromosome at the disease onset	Negative	205	168	(81.95)
	Positive	13	12	(92.31)
	Not tested	5	4	(80.00)
	Unknown	2	2	(100.00)
	NR	1	1	(100.00)
Treatment result before use of Evoltra (First remission induction therapy)	In Remission	171	134	(78.36)
	Not in remission	50	48	(96.00)
	Not done	3	3	(100.00)
	Unknown	2	2	(100.00)

Factors		N	N with ADRs	(%)
Total		226	187	(82.74)
Treatment history before use of Evoltra (Central nervous system-directed prevention therapy)	Not done	20	17	(85.00)
	Cranial radiotherapy	17	16	(94.12)
	Intrathecal injection	193	160	(82.90)
	Systemic chemotherapy	106	87	(82.08)
	Others	2	2	(100.00)

Treatment history before use of Evoltra (Hematopoietic stem cell transplantation)	No	131	114	(87.02)
	Yes	94	72	(76.60)
	NR	1	1	(100.00)
Re-remission induction therapy	Yes	187	157	(83.96)
	No	39	30	(76.92)
No. of re-remission induction therapy	None	39	30	(76.92)
	1	87	70	(80.46)
	2	59	50	(84.75)
	3	23	20	(86.96)
	≧4	18	17	(94.44)
Relapse	Yes	203	166	(81.77)
	No	22	20	(90.91)
	NR	1	1	(100.00)
Performance status (PS) immediately before Evoltra administration	0	94	71	(75.53)
	1	73	67	(91.78)
	2	31	24	(77.42)
	3	20	17	(85.00)
	4	7	7	(100.00)
	NR	1	1	(100.00)

N: number of patients
NR: Not reported

[Intensive survey items]

The ADRs of hematotoxicity, infection, renal disorders, Hepatobiliary disorders, capillary leak syndrome and systemic Inflammatory response syndrome, tumor lysis syndrome, and cardiovascular events were collected as intensive survey items. The incidence of ADRs of intensive survey items were shown in Table 4.

Table 4 Incidence of ADRs (intensive survey items)

Intensive survey items/PT	Clinical Trials ADRs *		Post-marketing survey CLOFAL06952 ADRs		Post-marketing survey CLOFAL06952 Serious ADRs	
	N	(%)	N	(%)	N	(%)
Total number of patients	7		260			
Haematotoxicity	6	(85.71)	184	(70.77)	144	(55.38)
Anaemia	4	(57.14)	88	(33.85)	43	(16.54)
Disseminated intravascular coagulation			2	(0.77)	1	(0.38)
Febrile neutropenia	3	(42.86)	66	(25.38)	52	(20.00)
Haemoglobin decreased	1	(14.29)	7	(2.69)	4	(1.54)
Leukopenia			5	(1.92)	3	(1.15)

Intensive survey items/PT	Clinical Trials ADRs *		Post-marketing survey CLOFAL06952 ADRs		Serious ADRs	
	N	(%)	N	(%)	N	(%)
Total number of patients	7		260			
Lymphocyte count decreased			7	(2.69)	5	(1.92)
Lymphocyte count increased						
Neutropenia	2	(28.57)	13	(5.00)	10	(3.85)
Neutrophil count decreased			69	(26.54)	47	(18.08)
Pancytopenia			6	(2.31)	4	(1.54)
Platelet count decreased	1	(14.29)	111	(42.69)	70	(26.92)
Thrombocytopenia	3	(42.86)	6	(2.31)	4	(1.54)
Thrombotic microangiopathy						
White blood cell count decreased			86	(33.08)	59	(22.69)
Histiocytosis haematophagic			1	(0.38)	1	(0.38)
Haematotoxicity			5	(1.92)	3	(1.15)
Bone marrow failure			11	(4.23)	11	(4.23)
Cytopenia			3	(1.15)	3	(1.15)
Infections	2	(28.57)	50	(19.23)	40	(15.38)
Bacteraemia			2	(0.77)	1	(0.38)
Bronchopulmonary aspergillosis			1	(0.38)	1	(0.38)
Cellulitis			2	(0.77)	1	(0.38)
Cytomegalovirus infection			1	(0.38)	1	(0.38)
Endotoxic shock			1	(0.38)	1	(0.38)
Escherichia sepsis			1	(0.38)	1	(0.38)
Fungal infection			1	(0.38)	1	(0.38)
Herpes zoster			6	(2.31)	4	(1.54)
Human herpesvirus 6 infection			1	(0.38)	1	(0.38)
Infection	1	(14.29)	6	(2.31)	4	(1.54)
Influenza						
Otitis externa						
Pneumonia			6	(2.31)	5	(1.92)
Pneumonia adenoviral			1	(0.38)	1	(0.38)
Pneumonia cytomegaloviral			1	(0.38)	1	(0.38)
Pneumonia respiratory syncytial viral						
Pulmonary mycosis			1	(0.38)		
Sepsis			15	(5.77)	13	(5.00)
Septic shock			1	(0.38)	1	(0.38)
Sinusitis	1	(14.29)				
Upper respiratory tract infection	1	(14.29)	1	(0.38)		
Varicella			1	(0.38)	1	(0.38)
Streptococcal sepsis			2	(0.77)	2	(0.77)

Intensive survey items/PT	Clinical Trials ADRs *		Post-marketing survey CLOFAL06952 ADRs		Serious ADRs	
	N	(%)	N	(%)	N	(%)
Total number of patients	7		260			
Systemic mycosis			1	(0.38)		
Klebsiella sepsis			1	(0.38)	1	(0.38)
Staphylococcal sepsis			1	(0.38)	1	(0.38)
Adenoviral haemorrhagic cystitis			1	(0.38)	1	(0.38)
Staphylococcal infection						
Enteritis infectious						
Cytomegalovirus viraemia			1	(0.38)	1	(0.38)
Viral haemorrhagic cystitis			1	(0.38)	1	(0.38)
Bacterial infection			1	(0.38)	1	(0.38)
Lung infection			1	(0.38)	1	(0.38)
Pleural infection			1	(0.38)	1	(0.38)
Respiratory syncytial virus infection			1	(0.38)	1	(0.38)
Biliary tract infection						
Device related infection			3	(1.15)	1	(0.38)
Cystitis viral			2	(0.77)	2	(0.77)
Aspergillus infection			1	(0.38)	1	(0.38)
Varicella zoster pneumonia			1	(0.38)	1	(0.38)
Renal disorders			9	(3.46)	8	(3.08)
Renal disorder						
Renal failure			1	(0.38)	1	(0.38)
Renal tubular disorder			1	(0.38)	1	(0.38)
Renal impairment			3	(1.15)	2	(0.77)
Acute kidney injury			5	(1.92)	5	(1.92)
Hepatobiliary disorders			38	(14.62)	23	(8.85)
Hepatic failure						
Hepatic function abnormal			23	(8.85)	14	(5.38)
Hepatic pain			1	(0.38)		
Hyperbilirubinaemia			1	(0.38)		
Jaundice			1	(0.38)	1	(0.38)
Liver disorder			10	(3.85)	5	(1.92)
Venoocclusive liver disease			1	(0.38)	1	(0.38)
Hepatobiliary disease			1	(0.38)	1	(0.38)
Drug-induced liver injury			1	(0.38)	1	(0.38)
Capillary leak syndrome			6	(2.31)	4	(1.54)
Capillary leak syndrome			6	(2.31)	4	(1.54)
Systemic inflammatory response syndrome			8	(3.08)	8	(3.08)
Systemic inflammatory response syndrome			8	(3.08)	8	(3.08)

Intensive survey items/PT	Clinical Trials ADRs *		Post-marketing survey CLOFAL06952 ADRs		Serious ADRs	
	N	(%)	N	(%)	N	(%)
Total number of patients	7		260			
Tumour lysis syndrome			10	(3.85)	7	(2.69)
Tumour lysis syndrome			10	(3.85)	7	(2.69)
Cardiacvascular events	2	(28.57)	4	(1.54)	4	(1.54)
Cardiac failure						
Cardiac failure congestive						
Electrocardiogram QT prolonged	1	(14.29)	1	(0.38)	1	(0.38)
Pericardial effusion	1	(14.29)	3	(1.15)	3	(1.15)
Tachycardia						

*: No serious ADRs were observed in clinical trials until NDA approval in Japan
N: number of patients
Blank: not observed
ADRs were categorized by the MedDRA ver. 22.1

[Safety in patients with specific backgrounds]
- In the pediatric patients (younger than 15 years old)
ADRs were observed in 104 out of the 124 patients (83.87%). The most common ADRs observed were platelet count decreased 45.16% (56/124 patients), anaemia 44.35% (55/124 patients), febrile neutropenia 36.29% (45/124 patients), white blood cell count decreased 34.68% (43/124 patients) and neutrophil count decreased 28.23% (35/124 patients).
-In the elderly patients (65 years old and older)
ADRs were observed in 11 out of the 12 patients (91.67%). The most common ADRs observed were platelet count decreased 58.33% (7/12 patients), neutrophil count decreased 41.67% (5/12 patients), white blood cell count decreased and anaemia 33.33% (4/12 patients) each, and febrile neutropenia 25.00% (3/12 patients).
-In the patients with renal function disorder
ADRs were observed in 7 out of the 10 patients (70.00%). The most common ADRs were hepatic function abnormal, platelet count decreased, neutrophil count decreased, febrile neutropenia and anaemia 20.00% (2/10 patients) each.
-In the patients with hepatic function disorder
ADRs were observed in 31 out of the 33 patients (93.94%). The most common ADRs were platelet count decreased 42.42% (14/33 patients), white blood cell count decreased 36.36% (12/33 patients), hepatic function abnormal and anaemia 18.18% (6/33 patients) each, alanine aminotransferase increased and febrile neutropenia 15.15% (5/33 patients) each.
-No pregnant patients were reported in this study.

Effectiveness
To evaluate the effectiveness, a modified version of the COG (Children's Oncology Group) standard was used, and the investigator judged it according to the following standard at the end of the final cycle. The effectiveness was evaluated by the best over-all response (CR, CRp or PR), and the effectiveness rate was evaluated by CR+CRp+PR.
Complete remission (CR): Meet all of the following conditions:
- No leukemic cells are found in the peripheral blood, and no extramedullary infiltration
- Less than 5% of leukemia cells in bone marrow
- Platelet count and neutrophil count in peripheral blood have recovered to ≧100,000/mm^3 and ≧1,000/mm3, respectively
Complete remission without recovery of platelet count (CRp):
- Meet all CR criteria except platelet count recovery (≧100,000/mm^3)
Partial remission (PR):
- No leukemic cells are found in peripheral blood

- Leukemic cells in bone marrow are 5% or more and 25% or less, and normal blood cell precursors are observed. Or if less than 5% of leukemic cells in bone marrow, but do not meet the criteria for CR and CRp

Ineffective: do not meet the criteria for CR, CRp and PR

The effectiveness analysis was performed for patients with “relapsed/refractory ALL aged 21 years or younger”, because the target population of clinical trials in Japan and overseas at the NDA submission in Japan was 21 years of age or younger. In addition, the effectiveness was also summarized for the patients aged 22 years and older.

Of the 225 patients subject to efficacy analysis, 139 patients were patients with “relapsed/refractory ALL aged 21 years or younger", and 138 patients, excluding the 1 non-evaluable case, were evaluated as "CR" 29.71% (41/138 cases), “CRp” 7.25% (10/138 cases), “PR” 10.87% (15/138 cases), and “Ineffective” 52.17% (72/138 cases). The “CR+CRp+PR” rate (effective rate) was 47.83% (66/138 cases) (Table 5).

Table 5 Effectiveness in patients with “relapsed/refractory ALL aged 21 years or younger" (Effectiveness analysis population, N=138)

	CR	CRp	PR	CR+CRp+PR	Ineffective	non-evaluable
N	41	10	15	66	72	1
(%)	29.71%	7.25%	10.87 %	47.83%	52.17%	-

In addition, 84 patients with “relapsed/refractory ALL aged 22 years or older” were evaluated as "CR" 4.76% (4/84 cases), “CRp” 7.14% (6/84 cases), “PR” 14.29% (12/84 cases), and “Ineffective” 73.81% (62/84 cases). The “CR+CRp+PR” rate (effective rate) was 26.19% (22/84 cases) (Table 6).

Table 6 Effectiveness in patients with “relapsed/refractory ALL aged 22 years or older" (Effectiveness analysis population, N=84)

	CR	CRp	PR	CR+CRp+PR	Ineffective
N	4	6	12	22	62
(%)	4.76%	7.14%	14.29 %	26.19%	73.81%

The effectiveness by factors possibly influencing the effectiveness in the patients with “relapsed/refractory ALL aged 21 years or younger” were shown in Table 7.

Table 7 Effectiveness by factors possibly influencing the effectiveness in patients with "relapsed/refractory ALL aged 21 years or younger" (effectiveness analysis population, N=138)

Factors		N	CR	CRp	PR	CR+CRp+PR		Ineffective	
			N	N	N	N	Rate (%)	N	Rate (%)
Total		138	41	10	15	66	(47.83)	72	(52.17)
Diagnosis (Reason for use)	Relapsed/ refractory ALL	138	41	10	15	66	(47.83)	72	(52.17)
Sex	Male	83	27	5	7	39	(46.99)	44	(53.01)
	Female	55	14	5	8	27	(49.09)	28	(50.91)
Previous medical history	Yes	46	12	6	4	22	(47.83)	24	(52.17)
	No	92	29	4	11	44	(47.83)	48	(52.17)
Complications	Yes	49	15	1	7	23	(46.94)	26	(53.06)
	No	89	26	9	8	43	(48.31)	46	(51.69)
Complication (Hepatic disorder)	Yes	12	3	1	1	5	(41.67)	7	(58.33)
	No	126	38	9	14	61	(48.41)	65	(51.59)
Complication (Renal disorder)	Yes	3	0	0	0	0	(0.00)	3	(100.00)
	No	135	41	10	15	66	(48.89)	69	(51.11)
No. of Evoltra treatment cycles	1 cycle	74	11	1	8	20	(27.03)	54	(72.97)
	2 cycles	47	22	8	6	36	(76.60)	11	(23.40)
	3 cycles	11	4	0	0	4	(36.36)	7	(63.64)
	4 cycles	2	2	0	0	2	(100.00)	0	(0.00)
	5 cycles	1	1	0	0	1	(100.00)	0	(0.00)
	6 cycles	3	1	1	1	3	(100.00)	0	(0.00)
Concomitant treatment for the target disease	Yes	112	37	10	12	59	(52.68)	53	(47.32)
	No	26	4	0	3	7	(26.92)	19	(73.08)
Hematopoietic stem cell transplantation	Yes	1	0	1	0	1	(100.00)	0	(0.00)
	No	137	41	9	15	65	(47.45)	72	(52.55)
Radiation therapy	Yes	1	0	1	0	1	(100.00)	0	(0.00)
	No	137	41	9	15	65	(47.45)	72	(52.55)
Concomitant medication for the target disease	Yes	112	37	10	12	59	(52.68)	53	(47.32)
	No	26	4	0	3	7	(26.92)	19	(73.08)

Factors		N	CR	CRp	PR	CR+CRp+PR		Ineffective	
			N	N	N	N	Rate (%)	N	Rate (%)
Total		138	41	10	15	66	(47.83)	72	(52.17)
Duration of the disease (year)	<1	36	8	3	1	12	(33.33)	24	(66.67)
	1≦ <3	57	12	4	7	23	(40.35)	34	(59.65)
	3≦ <5	24	8	2	4	14	(58.33)	10	(41.67)
	≧5	20	12	1	3	16	(80.00)	4	(20.00)
	Unknown	1	1	0	0	1	(100.00)	0	(0.00)
French-American-British (FAB) classification at the disease onset	L1	95	33	7	10	50	(52.63)	45	(47.37)
	L2	25	7	1	1	9	(36.00)	16	(64.00)
	L3	7	0	1	1	2	(28.57)	5	(71.43)
	Others	2	0	0	1	1	(50.00)	1	(50.00)
	Unknown	6	1	0	2	3	(50.00)	3	(50.00)
	NR	3	0	1	0	1	(33.33)	2	(66.67)
Type of leukemia cells at the disease onset	B cell	120	37	10	12	59	(49.17)	61	(50.83)
	T cell	12	2	0	1	3	(25.00)	9	(75.00)
	Others	6	2	0	2	4	(66.67)	2	(33.33)
Philadelphia chromosome at the disease onset	Negative	134	40	10	12	62	(46.27)	72	(53.73)
	Positive	2	1	0	1	2	(100.00)	0	(0.00)
	Unknown	2	0	0	2	2	(100.00)	0	(0.00)
Treatment result before use of Evoltra (First remission induction therapy)	In Remission	106	30	8	10	48	(45.28)	58	(54.72)
	Not in remission	27	9	2	3	14	(51.85)	13	(48.15)
	Not done	3	2	0	0	2	(66.67)	1	(33.33)
	Unknown	2	0	0	2	2	(100.00)	0	(0.00)
Treatment history before use of Evoltra (Central nervous system-directed preventive therapy)	Not done	10	2	0	0	2	(20.00)	8	(80.00)
	Cranial radiotherapy	11	3	1	2	6	(54.55)	5	(45.45)
	Intrathecal injection	122	38	10	13	61	(50.00)	61	(50.00)
	Systemic chemotherapy	79	23	5	8	36	(45.57)	43	(54.43)
	Others	2	0	0	2	2	(100.00)	0	(0.00)
Treatment history before use of Evoltra (Hematopoietic stem cell transplantation)	No	85	25	7	7	39	(45.88)	46	(54.12)
	Yes	52	16	3	7	26	(50.00)	26	(50.00)
	NR	1	0	0	1	1	(100.00)	0	(0.00)
Re-remission induction therapy	Yes	116	35	8	11	54	(46.55)	62	(53.45)
	No	22	6	2	4	12	(54.55)	10	(45.45)
No. of re-remission induction therapy	None	22	6	2	4	12	(54.55)	10	(45.45)
	1	56	20	4	3	27	(48.21)	29	(51.79)
	2	37	7	4	6	17	(45.95)	20	(54.05)
	3	16	7	0	1	8	(50.00)	8	(50.00)
	≧4	7	1	0	1	2	(28.57)	5	(71.43)

Factors		N	CR	CRp	PR	CR+CRp+PR		Ineffective	
			N	N	N	N	Rate (%)	N	Rate (%)
Total		138	41	10	15	66	(47.83)	72	(52.17)
Relapse	Yes	125	37	9	15	61	(48.80)	64	(51.20)
	No	13	4	1	0	5	(38.46)	8	(61.54)
Performance status (PS) immediately before Evoltra administration	0	65	27	5	8	40	(61.54)	25	(38.46)
	1	41	9	3	3	15	(36.59)	26	(63.41)
	2	15	1	1	2	4	(26.67)	11	(73.33)
	3	12	3	1	1	5	(41.67)	7	(58.33)
	4	4	1	0	1	2	(50.00)	2	(50.00)
	NR	1	0	0	0	0	(0.00)	1	(100.00)

N: number of patients
NR: Not reported

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