Clinical trial results:
A Phase I/II, Multi-Center, Open-Label, Repeat-Dose Study of Forodesine Hydrochloride Infusion in Patients with B-cell Acute Lymphoblastic Leukemia with an Option of Extended Use of Forodesine Hydrochloride

Summary

EudraCT number	2005-000627-42
Trial protocol	DE
Global end of trial date	27 March 2007

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	BCX1777-04-106

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00289562
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioCryst Pharmaceuticals Inc.
Sponsor organisation address	4505 Emperor Blvd., Suite 200, Durham, United States, NC 27703
Public contact	Study Director, BioCryst Pharmaceuticals Inc., 001 919-859-1302, clinicaltrials@biocryst.com
Scientific contact	Study Director, BioCryst Pharmaceuticals Inc., 001 919-859-1302, clinicaltrials@biocryst.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2007
Global end of trial reached?	Yes
Global end of trial date	27 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety of repeat doses of intravenous (IV) infusion of forodesine in patients with B-ALL, which under WHO Guidelines is now referred to as precursor B-lymphoblastic leukemia/lymphoma.

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, and in accordance with the Declaration of Helsinki. The informed consent form (ICF), protocol and amendments for this trial were submitted to and approved by an appropriate Independent Ethics Committee (IEC). Routine monitoring was performed to verify that rights and well-being of subjects were protected. Emergency equipment and medications were available within the clinical unit as per current standard procedures. Any medication considered necessary for the subject's safety and well-being was given at the discretion of the Investigator. A signed informed consent form (ICF) was obtained from each subject prior to performing any study-related procedures. The informed consent process took place under conditions where the subject had adequate time to consider the risks and benefits associated with his/her participation in the study. The Investigator explained to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	28
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	1
Adolescents (12-17 years)	1
Adults (18-64 years)	22
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were enrolled into the study after confirmation they satisfied the eligibility criteria including having failed at least 1 treatment regimen for B-ALL.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Forodesine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Forodesine
Investigational medicinal product code	
Other name	BCX1777
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In the initial treatment period, patients received 4 weeks of treatment with daily infusions of forodesine for 5 consecutive days with at least 2 non-treatment days, but no more than 4 non-treatment days per week. IV infusion of forodesine was given at a dose of 80 mg/m2 per day or 135 mg/m2 per day over 30 minutes. The IV forodesine dose could be reduced to 40 mg/m2 per day in the event of emerging toxicity. At the end of the Initial Treatment Period responding patients (CR, CRp, or PR) or patients who exhibited sufficient clinical activity went on to receive an additional 4 weeks of treatment with daily infusions of forodesine given at the same dose as the patient received during Initial Treatment Period.

Number of subjects in period 1	Forodesine
Started	28
Completed	6
Not completed	22
Adverse event, serious fatal	1
Bad Physical Condition	1
Consent withdrawn by subject	1
Lack of Response	1
Adverse event, non-fatal	2
Disease Progression	14
Initial Treatment Period only	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
Children (2-11 years)	1	1	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	22	22	
From 65-84 years	4	4	
Age continuous Units: years			
arithmetic mean	37.8		
standard deviation	± 20.54	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	18	18	
Number of Prior B-Cell Treatments Units: Subjects			
One	8	8	
Two	10	10	
Three	6	6	
Four	3	3	
Five	1	1	
Duration of B-cell Leukemia Units: Months			
arithmetic mean	21.4		
standard deviation	± 18.50	-	

End points

End points reporting groups

Reporting group title	Forodesine

Reporting group description: -

Primary: Safety and Tolerability, as Measured by the Number of Participants Experiencing Adverse Events.

End point title	Safety and Tolerability, as Measured by the Number of Participants Experiencing Adverse Events.[1]

End point description:

End point type	Primary

End point timeframe:

Adverse Events were recorded from consent until week 8 or study discontinuation

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing via statistical analysis was performed.

End point values	Forodesine			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: subjects				
Adverse Event	28			
Severe or Life Threatening Adverse Event	22			
Adverse Event Related to Study Drug	16			
Serious Adverse Event	19			
Adverse Event Leading to Discontinuation	16			
Adverse Event Leading to Death	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Response to Treatment

End point title	Disease Response to Treatment

End point description:

The primary efficacy endpoint was the proportion of patients with Complete Response (CR), Partial Response (PR) or Complete Response in Absence of Platelet Recovery (CRp) at the end of the Initial Treatment Period.

End point type	Secondary

End point timeframe:

End of Initial Treatment Period; 28 days

End point values	Forodesine			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: subjects				
Complete Response	1			
Complete Response in Absence of Platelet Recovery	0			
Partial Response	2			
non-Response	14			
Missing	11			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs were recorded from time of consent until week 8 or study discontinuation	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Forodesine
Reporting group description:	
The safety population included all subjects who received at least one dose/infusion of study treatment.	

Serious adverse events	Forodesine		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 28 (67.86%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	12		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Tremor			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 5		
Pyrexia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Multi-organ disorder			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 2		
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 2		
Urosepsis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Forodesine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	7		

Hypertension			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	11 / 28 (39.29%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Asthenia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Catheter placement			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Generalised oedema			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypothermia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	6		
Dyspnoea			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Hiccups			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Respiratory distress			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Atelectasis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Laryngeal pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 28 (42.86%)		
occurrences (all)	12		
Anxiety			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Confusional state			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Depression			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Weight decreased			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
blast count increased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	7		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	9		
Dizziness			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Lethargy			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Anaemia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Neutropenia			

subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Leukocytosis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Monocytopenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Ear discomfort			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Eye disorders			
Eye pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Eye swelling			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	10		
constipation			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	7 / 28 (25.00%)		
occurrences (all)	7		
Vomiting			

subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 5 3 / 28 (10.71%) 3 2 / 28 (7.14%) 2		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Skin hyperpigmentation subjects affected / exposed occurrences (all)	 7 / 28 (25.00%) 7 3 / 28 (10.71%) 3 2 / 28 (7.14%) 2 2 / 28 (7.14%) 2		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2 2 / 28 (7.14%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity	 5 / 28 (17.86%) 5 4 / 28 (14.29%) 4		

subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Hepatic infection fungal			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	6		
Hyperkalaemia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Fluid balance positive			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Anorexia nervosa			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2005	Due to the rapid response & the rapid rebound seen in some patients after being off treatment only a few days, all patients are offered forodesine administration 7 days a week. If required, an equivalent oral dose can be given up to 2 days per cycle. The 2-week rest periods between cycles 4 and 5 during the Initial Treatment Period and Long Term Follow up Period have been deleted. Concurrent dexamethasone therapy on Days 1-4 is no longer required. This has been changed to a rescue medication for blast crisis given according to the Investigator's discretion. The duration of therapy for the initial treatment period has changed from 4 cycles of treatment administered over a 6-week period to 4 weeks of continuous daily treatment. Bone marrow evaluations have been changed to the 4 week and 8 week time points to better correlate with the new dosing schedule. The Long Term Follow-Up Period is termed an Extended Treatment Period, includes an additional 4 weeks of treatment and is limited to subjects whose disease has not progressed at the end the first 4 weeks of treatment. Patients can receive further treatment by compassionate use. The response criteria in this study have been modified to follow the standard leukemia guidelines for response, including bone marrow results, evaluation of extramedullary disease and normalization of other peripheral blood components. The introduction has been updated to include new information from phase 1 and 2 clinical studies. The criteria for dose modifications have been revised to include dose modifications for possibly related grade 3 (non-hematologic) or grade 4 (hematologic and non-hematologic) AEs. The dose modification guidelines have been revised to include an initial dose reduction rather than a break in therapy for these toxicities.
08 July 2005	Clarification that the patient population allowed in this study, B-ALL patients, includes all disease subtypes under the newer terminology of precursor B-lymphoblastic leukemia/lymphoma, according to WHO guidelines for classification of leukemias. Addition of CD4+CD25+ to the panel of lymphocyte subpopulations analyzed for the study (as an optional assessment). Change study drug information, oral dose calculation, and number of capsules administered to reflect 100-mg final formulation. Clarify that adverse event and severe adverse event reporting (AE and SAE) begins after the patient has signed the informed consent document, rather than after administration of the first dose of study medication. Modification of Concomitant and Supportive Therapy section to state that patients with a CMV reactivation may be treated with empiric anti-CMV therapy, according to the Institution's standard of care Clarification of the processing and shipping guidelines for blood samples collected for PNP and ex-vivo sensitivity analyses.

18 October 2005	The dosing regimen has been redefined to include 5 days of intravenous study drug administration followed by 2 days but no more than 4 days of nontreatment. This change was necessary in an effort to obtain a more homogeneous study population for analysis. The intravenous dose has been changed from 135 mg/m2 to 80 mg/m2, since doses above 40 mg/m2 bid (total daily dose of 80 mg/m2) have not been shown to provide increases in the pharmacodynamic marker (dGuo) measured in previous studies. Guidelines for bone-marrow evaluation were clarified to include a second evaluation (i.e., "overread") by a central laboratory. Guidelines for continuing forodesine treatment past the Initial Treatment Period were clarified so that only patients showing sufficient clinical activity would continue treatment in the Extended Treatment Period. This is based on data showing that all patients who have responded to forodesine treatment in previous studies have shown evidence of clinical activity within 2-4 weeks of treatment. Response criteria were updated to include guidelines for assessing response in patients with lymphoblastic lymphoma. The interim analysis was deleted and study-stopping criteria were added instead, for patient safety. Eligibility criteria were modified to exclude patients from the study who may be hypersensitive or intolerant to study drug components. Definition of acceptable birth control to be used during the study was added for clarification. Dose-modification guidelines were revised to reflect the 80-mg/m2 dose. Sections regarding study drug information were updated to reflect new information and correct or clarify existing information. Revisions were made to the number of sites needed for the study.
01 November 2005	Clarification of items in the statistical section of the protocol regarding the stopping rules for the study and the basis for the sample size calculation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported