



Clinical trial results:

Intensified Tyrosine Kinase Inhibitor Therapy (Dasatinib: IND# 73969, NSC# 732517) in Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2010-022946-25
Trial protocol	Outside EU/EEA
Global end of trial date	05 March 2015

Results information

Result version number	v1 (current)
This version publication date	05 May 2017
First version publication date	05 May 2017

Trial information

Trial identification

Sponsor protocol code	AALL0622
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00720109
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Children's Oncology Group
Sponsor organisation address	222 E Huntington Dr, Suite 100, Monrovia, United States, 91016
Public contact	Peter C. Adamson - COG Group Chair, The Children's Hospital of Philadelphia, 1 (215) 590-6359, Adamson@email.chop.edu
Scientific contact	Peter C. Adamson - COG Group Chair, The Children's Hospital of Philadelphia, 1 (215) 590-6359, Adamson@email.chop.edu

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000567-PIP01-09
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	05 March 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to determine the feasibility and toxicity of dasatinib in combination with intensified chemotherapy in young patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia and to determine whether the intensification of tyrosine kinase inhibition (TKI) through the addition of dasatinib to induction therapy (on days 15-28) and the substitution of dasatinib for imatinib mesylate during post-induction therapy will lead to a 3-year event-free survival (EFS) in $\geq 60\%$ of these patients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

The CA180204 (COG AALL0622) chemotherapy backbone was administered by the investigating site's standard prescribing procedures according to country availability and specific regulatory requirements. Initially, to compensate for elimination of prophylactic cranial radiotherapy, intrathecal (IT) methotrexate (MTX) was changed to triple intrathecal therapy (ITT, consisting of cytarabine, MTX, and hydrocortisone) on day 29 of induction, and an additional dose of ITT was added on the first day of Consolidation 1. This increased the number of IT chemotherapy treatments from 18 to 20. Reductions in the chemotherapy backbone were implemented by Amendment during the course of the study. These changes were reduction of high-dose (HD) MTX infusions from 9 to 7 and reduction of IT chemotherapy administrations from 20 to 18.

Evidence for comparator: -

Actual start date of recruitment	01 July 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 56
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	New Zealand: 1
Worldwide total number of subjects	63
EEA total number of subjects	0

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)	3
Children (2-11 years)	37
Adolescents (12-17 years)	16
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 47 sites in 4 countries.

Pre-assignment

Screening details:

A total of 63 subjects were enrolled and 62 were treated. Reason for non-treatment was physician determined it was not in subject's best interest.

Period 1

Period 1 title	Induction Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dasatinib, discontinuous (Cohort 1)

Arm description:

Subjects in Cohort 1 (discontinuous dasatinib) received 70 weeks of dasatinib treatment (of the total of 131 weeks of chemotherapy). During induction (4 weeks) Dasatinib was administered during weeks 3-4. During consolidation (2 blocks of 3 weeks each) Dasatinib was administered during weeks 6-7, 9-10. During Re-Induction / Intensification Dasatinib was administered during weeks 12-13, 15-16, 18-19, 21-22, 24-25, 27-28, 30-31, 33-34. During Maintenance Dasatinib was administered during weeks 36-37, 40-41, 44-45, 48-49, 52-53, 56-57, 60-61, 64-65, 68-69, 72-73, 76-77, 80-81, 84-85, 88-89, 92-93, 96-97, 100-101, 104-105, 108-109, 112-113, 116-117, 120-121, 124-125, 128-129.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a dose of 60 mg/m² once daily (QD). If dasatinib at a dose of 60 mg/m² daily was not well tolerated, subjects received dasatinib treatment at 48 mg/m² daily. If necessary to permit administration in young children, the intact tablets could be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. mg=milligram

Arm title	Dasatinib, continuous (Cohort 2)
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Arm description:

Subjects in Cohort 2 (continuous dasatinib) received a total of 128 weeks of dasatinib treatment (of the 131 weeks of chemotherapy). During induction (4 weeks), Dasatinib was administered during weeks 3-4. During consolidation (2 blocks of 3 weeks each), Dasatinib was administered during weeks 6-11. During Re-Induction / Intensification, Dasatinib was administered during weeks 12-35. During Maintenance, Dasatinib was administered during weeks 36-131.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a dose of 60 mg/m² once daily (QD). If dasatinib at a dose of 60 mg/m² daily was not well tolerated, subjects received dasatinib treatment at 48 mg/m² daily. If

necessary to permit administration in young children, the intact tablets could be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. mg=milligram

Number of subjects in period 1^[1]	Dasatinib, discontinuous (Cohort 1)	Dasatinib, continuous (Cohort 2)
Started	40	22
Completed	22	12
Not completed	18	10
Physician decision	4	1
Adverse event, non-fatal	1	-
Subject ineligible	1	-
Bone marrow transplant therapy	11	7
Development of a second malignant neoplasm	-	1
Disease progression/relapse during treatment	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Out of 63 subjects who were enrolled only 62 subjects were treated.

Period 2

Period 2 title	Risk Stratification Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dasatinib, discontinuous (Cohort 1)

Arm description:

The Risk Stratification period followed the Induction period. During Risk Stratification, the minimal residual disease (MRD) classified subjects into risk groups. All High-Risk subjects and all Standard-Risk subjects with matched sibling donors were urged to proceed to hematopoietic stem cell transplant (HSCT). All subjects who did not proceed to HSCT continued on study and received chemotherapy plus Dasatinib. Subjects in Cohort 1 (discontinuous dasatinib) received 70 weeks of dasatinib treatment (of the total of 131 weeks of chemotherapy) during the Induction period.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a dose of 60 mg/m² once daily (QD). If dasatinib at a dose of 60 mg/m² daily was not well tolerated, subjects received dasatinib treatment at 48 mg/m² daily. If necessary to permit administration in young children, the intact tablets could be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. mg=milligram

Arm title	Dasatinib, continuous (Cohort 2)
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Arm description:

The Risk Stratification period followed the Induction period. During Risk Stratification, the minimal residual disease (MRD) was used to classify subjects into risk groups. All High-Risk subjects and all Standard-Risk subjects with matched sibling donors were urged to proceed to hematopoietic stem cell transplant (HSCT). All subjects who did not proceed to HSCT continued on study and received chemotherapy plus Dasatinib. Subjects in Cohort 2 (continuous dasatinib) received a total of 128 weeks of Dasatinib treatment (of the 131 weeks of chemotherapy) during the Induction period.

Arm type	Experimental
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Dasatinib tablets orally at a dose of 60 mg/m² once daily (QD). If dasatinib at a dose of 60 mg/m² daily was not well tolerated, subjects received dasatinib treatment at 48 mg/m² daily. If necessary to permit administration in young children, the intact tablets could be placed (and allowed to dissolve) in 1 ounce of lemonade (a double strength juice is recommended to obscure the bitter taste), or 1 ounce of preservative-free apple juice, or 1 ounce of preservative-free orange juice. mg=milligram

Number of subjects in period 2	Dasatinib, discontinuous (Cohort 1)	Dasatinib, continuous (Cohort 2)
Started	22	12
Completed	29	15
Not completed	11	7
Not eligible	2	1
Death	4	4
Lost to follow-up	-	1
Enrolled to another study with therapeutic intent	5	1
Joined	18	10
Treatment not completed, but stratified for risk	18	10

Baseline characteristics

Reporting groups

Reporting group title	Dasatinib, discontinuous (Cohort 1)
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Reporting group description:

Subjects in Cohort 1 (discontinuous dasatinib) received 70 weeks of dasatinib treatment (of the total of 131 weeks of chemotherapy). During induction (4 weeks) Dasatinib was administered during weeks 3-4. During consolidation (2 blocks of 3 weeks each) Dasatinib was administered during weeks 6-7, 9-10. During Re-Induction / Intensification Dasatinib was administered during weeks 12-13, 15-16, 18-19, 21-22, 24-25, 27-28, 30-31, 33-34. During Maintenance Dasatinib was administered during weeks 36-37, 40-41, 44-45, 48-49, 52-53, 56-57, 60-61, 64-65, 68-69, 72-73, 76-77, 80-81, 84-85, 88-89, 92-93, 96-97, 100-101, 104-105, 108-109, 112-113, 116-117, 120-121, 124-125, 128-129.

Reporting group title	Dasatinib, continuous (Cohort 2)
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Reporting group description:

Subjects in Cohort 2 (continuous dasatinib) received a total of 128 weeks of dasatinib treatment (of the 131 weeks of chemotherapy). During induction (4 weeks), Dasatinib was administered during weeks 3-4. During consolidation (2 blocks of 3 weeks each), Dasatinib was administered during weeks 6-11. During Re-Induction / Intensification, Dasatinib was administered during weeks 12-35. During Maintenance, Dasatinib was administered during weeks 36-131.

Reporting group values	Dasatinib, discontinuous (Cohort 1)	Dasatinib, continuous (Cohort 2)	Total
Number of subjects	40	22	62
Age categorical			
Number of participants categorized by age at diagnosis (years)			
Units: Subjects			
> 1 - < 2 years	1	2	3
>=2 - < 7 years	14	5	19
>=7 - < 12 years	11	7	18
>=12 - < 18 years	9	6	15
>=18 years	5	2	7
Age continuous			
Mean age at diagnosis (years)			
Units: years			
arithmetic mean	9.9	10.3	
standard deviation	± 6.2	± 6.07	-
Gender categorical			
Units: Subjects			
Female	14	6	20
Male	26	16	42
Immunophenotype			
Units: Subjects			
B-precursor	36	22	58
T-cell	4	0	4
Acute leukemia, indeterminate lineage	0	0	0
Time from diagnosis to first Dasatinib dosing day			
Units: days			
median	17	17	
full range (min-max)	14 to 33	14 to 26	-
Peripheral White Blood Cell			

Units: 10**3/microliter arithmetic mean standard deviation	95.3 ± 146.64	87.3 ± 126.77	-
Peripheral Blast Count Units: percentage arithmetic mean standard deviation	40.8 ± 33.43	48.8 ± 33.58	-
Peripheral Platelet Count Units: 10**3/microliter arithmetic mean standard deviation	1213.7 ± 7101.33	96.3 ± 87.05	-

Subject analysis sets

Subject analysis set title	Standard-Risk Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description: Standard-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with a bone marrow status M1 (< 5% lymphoblasts; complete response in bone marrow) and with minimal residual disease (MRD) < 1% at the end of Induction and MRD < 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	High-Risk Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description: High-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with minimal residual disease (MRD) ≥ 1% at the end of Induction or MRD ≥ 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	Standard-Risk Cohort 1
Subject analysis set type	Sub-group analysis
Subject analysis set description: Standard-Risk Cohort 1 is defined as the population of subjects in Cohort 1 with a bone marrow status M1 (< 5% lymphoblasts; complete response in bone marrow) and with minimal residual disease (MRD) < 1% at the end of Induction and MRD < 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	High-Risk Cohort 1
Subject analysis set type	Sub-group analysis
Subject analysis set description: High-Risk Cohort 1 is defined as the population of subjects in Cohort 1 with minimal residual disease (MRD) ≥ 1% at the end of Induction or MRD ≥ 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	Any Risk, Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description: Any Risk Cohort 2 combines the population of subjects in Standard-Risk Cohort 2 and High-Risk Cohort 2. Standard-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with a bone marrow status M1 (< 5% lymphoblasts; complete response in bone marrow) and with minimal residual disease (MRD) < 1% at the end of Induction and MRD < 0.01% at the end of Consolidation Block 2. High-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with minimal residual disease (MRD) ≥ 1% at the end of Induction or MRD ≥ 0.01% at the end of Consolidation Block 2.	

Reporting group values	Standard-Risk Cohort 2	High-Risk Cohort 2	Standard-Risk Cohort 1
Number of subjects	17	4	31
Age categorical			
Number of participants categorized by age at diagnosis (years)			
Units: Subjects			
> 1 - < 2 years	99999	99999	99999
>=2 - < 7 years	99999	99999	99999
>=7 - < 12 years	99999	99999	99999

>=12 - < 18 years	99999	99999	99999
>=18 years	99999	99999	99999

Age continuous			
Mean age at diagnosis (years)			
Units: years			
arithmetic mean	120	120	120
standard deviation	± 99999.9	± 99999.9	± 99999.9
Gender categorical			
Units: Subjects			
Female	99999	99999	99999
Male	99999	99999	99999
Immunophenotype			
Units: Subjects			
B-precursor	99999	99999	99999
T-cell	99999	99999	99999
Acute leukemia, indeterminate lineage	99999	99999	99999
Time from diagnosis to first Dasatinib dosing day			
Units: days			
median	99999	99999	99999
full range (min-max)	-0.99999 to 99999	-0.99999 to 99999	-0.99999 to 99999
Peripheral White Blood Cell			
Units: 10**3/microliter			
arithmetic mean	99999	99999	99999
standard deviation	± 99999.9	± 99999.9	± 99999.9
Peripheral Blast Count			
Units: percentage			
arithmetic mean	99999	99999	99999
standard deviation	± 99999.9	± 99999.9	± 99999.9
Peripheral Platelet Count			
Units: 10**3/microliter			
arithmetic mean	99999	99999	99999
standard deviation	± 99999.9	± 99999.9	± 99999.9

Reporting group values	High-Risk Cohort 1	Any Risk, Cohort 2	
Number of subjects	5	21	
Age categorical			
Number of participants categorized by age at diagnosis (years)			
Units: Subjects			
> 1 - < 2 years	99999	99999	
>=2 - < 7 years	99999	99999	
>=7 - < 12 years	99999	99999	
>=12 - < 18 years	99999	99999	
>=18 years	99999	99999	
Age continuous			
Mean age at diagnosis (years)			
Units: years			
arithmetic mean	120	120	
standard deviation	± 99999.9	± 99999.9	

Gender categorical Units: Subjects			
Female	99999	99999	
Male	99999	99999	
Immunophenotype Units: Subjects			
B-precursor	99999	99999	
T-cell	99999	99999	
Acute leukemia, indeterminate lineage	99999	99999	
Time from diagnosis to first Dasatinib dosing day Units: days			
median	99999	99999	
full range (min-max)	-0.99999 to 99999	-0.99999 to 99999	
Peripheral White Blood Cell Units: 10**3/microliter			
arithmetic mean	99999	99999	
standard deviation	± 99999.9	± 99999.9	
Peripheral Blast Count Units: percentage			
arithmetic mean	99999	99999	
standard deviation	± 99999.9	± 99999.9	
Peripheral Platelet Count Units: 10**3/microliter			
arithmetic mean	99999	99999	
standard deviation	± 99999.9	± 99999.9	

End points

End points reporting groups

Reporting group title	Dasatinib, discontinuous (Cohort 1)
Reporting group description:	
Subjects in Cohort 1 (discontinuous dasatinib) received 70 weeks of dasatinib treatment (of the total of 131 weeks of chemotherapy). During induction (4 weeks) Dasatinib was administered during weeks 3-4. During consolidation (2 blocks of 3 weeks each) Dasatinib was administered during weeks 6-7, 9-10. During Re-Induction / Intensification Dasatinib was administered during weeks 12-13, 15-16, 18-19, 21-22, 24-25, 27-28, 30-31, 33-34. During Maintenance Dasatinib was administered during weeks 36-37, 40-41, 44-45, 48-49, 52-53, 56-57, 60-61, 64-65, 68-69, 72-73, 76-77, 80-81, 84-85, 88-89, 92-93, 96-97, 100-101, 104-105, 108-109, 112-113, 116-117, 120-121, 124-125, 128-129.	
Reporting group title	Dasatinib, continuous (Cohort 2)
Reporting group description:	
Subjects in Cohort 2 (continuous dasatinib) received a total of 128 weeks of dasatinib treatment (of the 131 weeks of chemotherapy). During induction (4 weeks), Dasatinib was administered during weeks 3-4. During consolidation (2 blocks of 3 weeks each), Dasatinib was administered during weeks 6-11. During Re-Induction / Intensification, Dasatinib was administered during weeks 12-35. During Maintenance, Dasatinib was administered during weeks 36-131.	
Reporting group title	Dasatinib, discontinuous (Cohort 1)
Reporting group description:	
The Risk Stratification period followed the Induction period. During Risk Stratification, the minimal residual disease (MRD) classified subjects into risk groups. All High-Risk subjects and all Standard-Risk subjects with matched sibling donors were urged to proceed to hematopoietic stem cell transplant (HSCT). All subjects who did not proceed to HSCT continued on study and received chemotherapy plus Dasatinib. Subjects in Cohort 1 (discontinuous dasatinib) received 70 weeks of dasatinib treatment (of the total of 131 weeks of chemotherapy) during the Induction period.	
Reporting group title	Dasatinib, continuous (Cohort 2)
Reporting group description:	
The Risk Stratification period followed the Induction period. During Risk Stratification, the minimal residual disease (MRD) was used to classify subjects into risk groups. All High-Risk subjects and all Standard-Risk subjects with matched sibling donors were urged to proceed to hematopoietic stem cell transplant (HSCT). All subjects who did not proceed to HSCT continued on study and received chemotherapy plus Dasatinib. Subjects in Cohort 2 (continuous dasatinib) received a total of 128 weeks of Dasatinib treatment (of the 131 weeks of chemotherapy) during the Induction period.	
Subject analysis set title	Standard-Risk Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Standard-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with a bone marrow status M1 (< 5% lymphoblasts; complete response in bone marrow) and with minimal residual disease (MRD) < 1% at the end of Induction and MRD < 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	High-Risk Cohort 2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
High-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with minimal residual disease (MRD) ≥ 1% at the end of Induction or MRD ≥ 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	Standard-Risk Cohort 1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Standard-Risk Cohort 1 is defined as the population of subjects in Cohort 1 with a bone marrow status M1 (< 5% lymphoblasts; complete response in bone marrow) and with minimal residual disease (MRD) < 1% at the end of Induction and MRD < 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	High-Risk Cohort 1
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
High-Risk Cohort 1 is defined as the population of subjects in Cohort 1 with minimal residual disease (MRD) ≥ 1% at the end of Induction or MRD ≥ 0.01% at the end of Consolidation Block 2.	
Subject analysis set title	Any Risk, Cohort 2

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Any Risk Cohort 2 combines the population of subjects in Standard-Risk Cohort 2 and High-Risk Cohort 2.	
Standard-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with a bone marrow status M1 (< 5% lymphoblasts; complete response in bone marrow) and with minimal residual disease (MRD) < 1% at the end of Induction and MRD < 0.01% at the end of Consolidation Block 2.	
High-Risk Cohort 2 is defined as the population of subjects in Cohort 2 with minimal residual disease (MRD) ≥ 1% at the end of Induction or MRD ≥ 0.01% at the end of Consolidation Block 2.	

Primary: Percent of Standard Risk Cohort 2 Subjects with 3-Year Event Free Survival (EFS)

End point title	Percent of Standard Risk Cohort 2 Subjects with 3-Year Event Free Survival (EFS) ^[1]
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End point description:

EFS = time from entry on study until an event occurred. Events for EFS = first occurrence of the following: induction failure, relapse at any site, secondary malignancy, or death.

Induction failure = disease progression during Induction. A bone marrow evaluation took place at the end of Induction, and disease progression was concluded if the lymphoblast count was > 25% (M3 bone marrow status).

Relapse = any recurrence of disease, whether in the marrow or extramedullary site: - Central Nervous System (CNS) relapse: Positive cytomorphology and 5 or more white blood cells/microliter in cerebral spinal fluid, or any signs of CNS leukemia such a facial nerve palsy, brain/eye involvement, or hypothalamic syndrome. - Testicular relapse: Must be documented by testicular biopsy, in the absence of concomitant bone marrow relapse. - Bone marrow relapse: Subjects with M3 marrow (>25% blasts) at any point after the beginning of re-Induction.

A 1-sided 95% confidence interval was reported.

End point type	Primary
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End point timeframe:

Day 1 up to Year 3

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: Only descriptive summary statistics were planned for this outcome measure.

End point values	Standard-Risk Cohort 2			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: percent of subjects				
number (confidence interval 95%)	70.1 (51.8 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects with 3-Year Event Free Survival (EFS)

End point title	Percent of Subjects with 3-Year Event Free Survival (EFS)
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End point description:

EFS = time from entry on study until an event occurred. Events for EFS = first occurrence of the following: induction failure, relapse at any site, secondary malignancy, or death.

Induction failure = disease progression during Induction. A bone marrow evaluation took place at the end of Induction, and disease progression was concluded if the lymphoblast count was > 25% (M3 bone marrow status).

Relapse = any recurrence of disease, whether in the marrow or extramedullary site: - Central Nervous System (CNS) relapse: Positive cytomorphology and 5 or more white blood cells/microliter in cerebral

spinal fluid, or any signs of CNS leukemia such a facial nerve palsy, brain/eye involvement, or hypothalamic syndrome. - Testicular relapse: Must be documented by testicular biopsy, in the absence of concomitant bone marrow relapse. - Bone marrow relapse: Subjects with M3 marrow (>25% blasts) at any point after the beginning of re-Induction.

A 1-sided 95% confidence interval was reported.

End point type	Secondary
End point timeframe:	
Day 1 up to Year 3	

End point values	Dasatinib, discontinuous (Cohort 1)	Dasatinib, continuous (Cohort 2)	High-Risk Cohort 2	Standard-Risk Cohort 1
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	21	4	31
Units: Percent of subjects				
number (confidence interval 95%)	86.6 (77.8 to 100)	66.3 (49.4 to 100)	50 (8.9 to 100)	90.3 (81.6 to 100)

End point values	High-Risk Cohort 1			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Percent of subjects				
number (confidence interval 95%)	80 (50.6 to 100)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects in Cohort 2 with Minimal Residual Disease (MRD) at the End of Induction

End point title	Percent of Subjects in Cohort 2 with Minimal Residual Disease (MRD) at the End of Induction ^[2]
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End point description:

Minimal residual disease levels were the proportion of leukemic cells in a sample at a specific time point. Percentage MRD was also categorized as follows: < 0.01%, 0.01%-0.099%, and >= 0.1%.

MRD-positive was defined as having a minimal residual disease > 0.01%. Induction therapy was conducted between days 15-28. A 1-sided 95% confidence interval was reported.

End point type	Secondary
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End point timeframe:

Week 4

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the specified arms was planned to be reported for this outcome measure.

End point values	Dasatinib, continuous (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Percent of Subjects				
number (confidence interval 95%)	52.4 (31 to 73.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects in Cohort 2 with Minimal Residual Disease (MRD) at the End of Consolidation

End point title	Percent of Subjects in Cohort 2 with Minimal Residual Disease (MRD) at the End of Consolidation ^[3]
End point description: Minimal residual disease levels were the proportion of leukemic cells in a sample at a specific time point. Percentage MRD was also categorized as follows: < 0.01%, 0.01%-0.099%, and ≥ 0.1%. MRD-positive was defined as having a minimal residual disease > 0.01%. Consolidation therapy in Cohort 2 was conducted between weeks 6-11. A 1-sided 95% confidence interval was reported.	
End point type	Secondary
End point timeframe: Week 11	

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only the specified arms was planned to be reported for this outcome measure.

End point values	Dasatinib, continuous (Cohort 2)			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Percent of subjects				
number (confidence interval 95%)	19 (8.9 to 36.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects with Overall Survival (OS) at Year 3

End point title	Percent of Subjects with Overall Survival (OS) at Year 3
End point description: Overall survival was defined as time in months from the date of entry on study to the date of death due to any cause. Subjects who had not died or who were lost to follow-up were censored on the last date the subject was known to be alive. A 1-sided 95% confidence interval was reported.	
End point type	Secondary

End point timeframe:

Year 3

End point values	Standard-Risk Cohort 2	Any Risk, Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	21		
Units: Percent of subjects				
number (confidence interval 95%)	93.8 (82.3 to 100)	90.2 (77.5 to 100)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 1st dose date through last dose date plus 30 days (approx. 3 years)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Dasatinib
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Reporting group description:

Dasatinib

Serious adverse events	Dasatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 62 (46.77%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis/thrombosis/embolism			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Headache			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Creatinine increased			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Hypotension			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left Ventricular Systolic Dysfunction			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
QTc Prolongation			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ifosfamide neurotoxicity			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mood alteration - agitation			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurology - Motor			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neurology - Sensory			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Personality/Behavioral			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Edema limb			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Hemorrhage			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Renal dysfunction			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis infectious			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile Neutropenia			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Periorbital infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper airway infection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Albumin - serum low			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Dasatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 62 (95.16%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 62 (38.71%)		
occurrences (all)	47		
Blood bilirubin increased			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Alanine aminotransferase increased			
subjects affected / exposed	35 / 62 (56.45%)		
occurrences (all)	137		
Neutrophil count decreased			
subjects affected / exposed	37 / 62 (59.68%)		
occurrences (all)	135		
Gamma-Glutamyltransferase increased			

subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	7		
Platelet count decreased			
subjects affected / exposed	27 / 62 (43.55%)		
occurrences (all)	73		
White blood cell count decreased			
subjects affected / exposed	17 / 62 (27.42%)		
occurrences (all)	73		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	4 / 62 (6.45%)		
occurrences (all)	5		
Hypertension			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	6		
Hypotension			
subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	13		
Nervous system disorders			
Convulsion			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	11		
Peripheral motor neuropathy			
subjects affected / exposed	10 / 62 (16.13%)		
occurrences (all)	19		
Peripheral sensory neuropathy			
subjects affected / exposed	11 / 62 (17.74%)		
occurrences (all)	18		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 62 (25.81%)		
occurrences (all)	59		
Febrile neutropenia			

subjects affected / exposed occurrences (all)	42 / 62 (67.74%) 151		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 7		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) Anaphylactic reaction subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4 4 / 62 (6.45%) 5		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Colitis subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Neutropenic colitis subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5 5 / 62 (8.06%) 6 10 / 62 (16.13%) 13 9 / 62 (14.52%) 25 5 / 62 (8.06%) 5 19 / 62 (30.65%) 26 10 / 62 (16.13%) 16		
Respiratory, thoracic and mediastinal disorders			

Hypoxia subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 7		
Infections and infestations Enterocolitis infectious subjects affected / exposed occurrences (all) Cellulitis subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all) Otitis media subjects affected / exposed occurrences (all) Skin infection subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Sepsis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	8 / 62 (12.90%) 18 5 / 62 (8.06%) 7 5 / 62 (8.06%) 7 5 / 62 (8.06%) 9 9 / 62 (14.52%) 10 8 / 62 (12.90%) 9 23 / 62 (37.10%) 37 7 / 62 (11.29%) 7 5 / 62 (8.06%) 13		
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	12		
Dehydration			
subjects affected / exposed	8 / 62 (12.90%)		
occurrences (all)	9		
Hyperglycaemia			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	9		
Hypoalbuminaemia			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	32 / 62 (51.61%)		
occurrences (all)	68		
Hypocalcaemia			
subjects affected / exposed	7 / 62 (11.29%)		
occurrences (all)	9		
Hyponatraemia			
subjects affected / exposed	12 / 62 (19.35%)		
occurrences (all)	16		
Hypophosphataemia			
subjects affected / exposed	5 / 62 (8.06%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported